Restylane® *Printer-Friendly Version**

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

Description

Restylane® is a gel of hyaluronic acid generated by Streptococcus species of bacteria, chemically crosslinked with BDDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/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 patients with bleeding disorders.
- *Restylane*® is contraindicated for implantation in anatomical spaces other than the dermis.

Warnings

- Defer 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 until the process has been controlled.
- Injection site reactions (e.g., swelling, redness, tenderness, or pain) to *Restylane*® have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the adverse experiences section for details.
- *Restylane*® must not be implanted into blood vessels. Localized superficial necrosis may occur after injection in or near dermal vessels, such as the glabellar area. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules that may occur rarely should be considered and treated as a soft tissue infection.

Precautions

- *Restylane*® is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on U.S. clinical studies, patients should be limited to 6.0 mL per patient per treatment. 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.
- As with all transcutaneous procedures, *Restylane*® implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety and efficacy of *Restylane*® for lip augmentation has not been established.
- The safety of *Restylane*® for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- Formation of keloids may occur after dermal filler injections including *Restylane*®. Keloid formation was not observed in studies involving 430 patients (including 151 African-Americans and 37 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, and 31GE0003 in the Clinical Trials Section.
- *Restylane*® injection may cause hyperpigmentation at the injection site. In a clinical study of 150 subjects with pigmented skin (of African-American heritage and Fitzpatrick Skin Types IV, V, and VI), the incidence of post-inflammatory hyperpigmentation was 9% (14/150). 50% of these events lasted up to six weeks after initial implantation.
- *Restylane*® should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at *Restylane*® injection sites. *Restylane*® should be used with caution in patients who have undergone therapy with thrombolytics, anticoagulants, or inhibitors of platelet aggregation in the preceding 3 weeks.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of *Restylane*® with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme cold weather at least 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.
- Injection of *Restylane*® into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- *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 1-800-555-5115. Glass is subject to breakage under a variety of unavoidable conditions. Care should be taken with the handling of the glass syringe and with disposing of broken glass to avoid laceration or other injury.
- *Restylane*® should not be mixed with other products before implantation of the device.

Adverse Experiences

There were four U.S. studies that reported adverse experiences.

In three U.S. studies (i.e., Study MA-1400-01, Study MA-1400-02, and 31GE0003) involving 430 patients at 33 centers, the adverse outcomes reported in patient diaries during 14 days after treatment are presented in Tables 1–6. The physician diagnosed adverse events identified in studies MA-1400-01 and MA-1400-02 at 72 hours after injection are presented in Table 7. In study 31GE0003, 138 patients at 6 centers received *Restylane*® injections in 1 side of the face and a bovine collagen dermal filler (Zyplast®) in the other side of the face. In Study MA-1400-01, 150 patients were injected with *Restylane*® on one side of the face and *Perlane*® on the other side of the face. In study MA-1400-02, 283 patients were randomized to receive either *Restylane*® or *Perlane*® injection on both sides of the face. Table 8 presents all investigator-identified adverse experiences recorded at study visits 2 weeks or more after injection in studies MA-1400-01, MA-1400-02, and 31GE0003.

In the fourth U.S. study (MA-004-03) involving 75 patients at 3 centers, adverse events reported by *Restylane*® patients are presented in Table 9. Patients in the study received *Restylane*® injections in both nasolabial folds at baseline, a second treatment in one nasolabial fold at 4.5 months and in the contralateral nasolabial fold at 9 months.

Table 1. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study 31GE0003)[1]

	Restylane® side	Zyplast® side	*Restylane*® side				Zyplast® side			
	Total patients reporting symptoms n (%)	Total patients 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%)	1 (0.7%)
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%)	8 (5.8%)
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%)	2 (1.4%)
Pain	79 (57.2%)	58 (42.0%)	55 (39.9%)	40 (29.0%)	34 (24.6%)	5 (3.6%)	76 (55.1%)	46 (33.3%)	10 (7.2%)	2 (1.4%)
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%)	2 (1.4%)
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%)	0 (0.0%)
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%)	3 (2.2%)

[1] 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 (Study 31GE0003)

	Restylane® side	Zyplast® side	*Restylane*® side				Zyplast® side			
	Total patients reporting symptoms n (%)	Total patients 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. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-02)[1]

	Restylane®	*Perlane*®	*Restylane*® Patients				*Perlane*® Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]	None	Tolerable[2]	Affected Daily Activity[2]	Disabling[2]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	111 (78.2%)	122 (86.5%)	28 (20.1%)	82 (59%)	28 (20.1%)	1 (0.7%)	17 (12.2%)	97 (69.8%)	24 (17.3%)	1 (0.7%)
Redness	114 (80.3%)	118 (83.7%)	25 (18%)	96 (69.1%)	17 (12.2%)	1 (0.7%)	21 (15.1%)	105 (75.5%)	12 (8.6%)	1 (0.7%)
Swelling	127 (89.4%)	128 (90.8%)	12 (8.6%)	102 (73.4%)	23 (16.5%)	2 (1.4%)	11 (7.9%)	107 (77%)	19 (13.7%)	2 (1.4%)
Pain	108 (76.1%)	114 (80.9%)	31 (22.3%)	93 (66.9%)	14 (10.1%)	1 (0.7%)	25 (18%)	96 (69.1%)	18 (12.9%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	16 (11.5%)	109 (78.4%)	12 (8.6%)	2 (1.4%)	9 (6.5%)	112 (80.6%)	18 (12.9%)	0 (0%)
Itching	67 (47.2%)	45 (31.9%)	72 (51.8%)	66 (47.5%)	1 (0.7%)	0 (0%)	94 (67.6%)	40 (28.8%)	3 (2.2%)	2 (1.4%)
Other[3]	3 (2.1%)	1 (0.7%)	NA	NA	NA	NA	NA	NA	NA	NA

[1] Missing values are not reported.
[2] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[3] Two patients reported pimples (one *Perlane*®/one *Restylane*®); one *Restylane*® patient reported a sore throat; one *Restylane*® patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 4. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-02)[1]

	Restylane® Patients	*Perlane*® Patients	*Restylane*® Patients				*Perlane*® Patients			
	Total Patients reporting symptoms n (%)	Total Patients reporting symptoms n (%)	Number of days[2]				Number of days[2]			
			1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	111 (78.2%)	122 (86.5%)	9 (8.1%)	69 (62.2%)	30 (27%)	3 (2.7%)	6 (4.9%)	81 (66.4%)	28 (23%)	7 (5.7%)
Redness	114 (80.3%)	118 (83.7%)	31 (27.2%)	71 (62.3%)	9 (7.9%)	3 (2.6%)	19 (16.1%)	87 (73.7%)	8 (6.8%)	4 (3.4%)
Swelling	127 (89.4%)	128 (90.8%)	12 (9.4%)	93 (73.2%)	19 (15.0%)	3 (2.4%)	6 (4.7%)	100 (78.1%)	17 (13.3%)	5 (3.9%)
Pain	108 (76.1%)	114 (80.9%)	37 (34.3%)	69 (63.9%)	2 (1.9%)	0 (0%)	46 (40.4%)	66 (57.9%)	2 (1.8%)	0 (0%)
Tenderness	123 (86.6%)	130 (92.2%)	21 (17.1%)	92 (74.8%)	9 (7.3%)	1 (0.8%)	24 (18.5%)	89 (68.5%)	16 (12.3%)	1 (0.8%)
Itching	67 (47.2%)	45 (31.9%)	22 (32.8%)	38 (56.7%)	6 (9.0%)	1 (1.5%)	19 (42.2%)	23 (51.1%)	3 (6.7%)	0 (0%)
Other[3]	3 (2.1%)	1 (0.7%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[2] Data are cumulated from up to four injection sites per patient with earliest and latest time point for any reaction provided.
[3] Two patients reported pimples (one *Perlane*®/one *Restylane*®); one *Restylane*® patient reported a sore throat; one *Restylane*® patient reported a runny nose; degree of disability was not reported for any of the four events.

Table 5. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-01)[1,2]

	Restylane®	*Perlane*®	*Restylane*® Patients				*Perlane*® Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]	None	Tolerable[3]	Affected Daily Activity[3]	Disabling[3]
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	70 (46.7%)	74 (49.3%)	79 (53%)	66 (44.3%)	4 (2.7%)	0 (0%)	75 (50.3%)	67 (45%)	7 (4.7%)	0 (0%)
Redness	87 (58%)	92 (61.3%)	62 (41.6%)	81 (54.4%)	6 (4%)	0 (0%)	57 (38.3%)	85 (57%)	7 (4.7%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	24 (16.1%)	109 (73.2%)	14 (9.4%)	2 (1.3%)	28 (18.8%)	108 (72.5%)	11 (7.4%)	2 (1.3%)
Pain	96 (64%)	103 (68.7%)	53 (35.6%)	84 (56.4%)	11 (7.4%)	1 (0.7%)	46 (30.9%)	90 (60.4%)	12 (8.1%)	1 (0.7%)
Tenderness	122 (81.3%)	130 (86.7%)	27 (18.1%)	110 (73.8%)	11 (7.4%)	1 (0.7%)	19 (12.8%)	116 (77.9%)	13 (8.7%)	1 (0.7%)
Itching	53 (35.3%)	58 (38.7%)	96 (64.4%)	49 (32.9%)	4 (2.7%)	0 (0%)	91 (61.1%)	54 (36.2%)	4 (2.7%)	0 (0%)
Other[4]	3 (2%)	3 (2%)	NA	3 (100%)	0 (%)	0 (%)	NA	3 (100%)	0 (%)	0 (%)

[1] Missing values are not reported.
[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.
[3] Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.
[4] Two patients reported mild transient headache and one patient reported mild 'twitching'; neither could be associated with a particular product.

Table 6. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-01)[1,2]

	Restylane® Patients	*Perlane*® Patients	*Restylane*® Patients				*Perlane*® Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days[3]				Number of days[3]			
			1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)	1 n (%)	2–7 n (%)	8–13 n (%)	14 n (%)
Bruising	70 (46.7%)	74 (49.3%)	13 (18.6%)	51 (72.9%)	6 (8.6%)	0 (0%)	23 (31.1%)	44 (59.5%)	6 (8.1%)	1 (1.4%)
Redness	87 (58%)	92 (61.3%)	33 (37.9%)	52 (59.8%)	2 (2.3%)	0 (0%)	38 (41.3%)	52 (56.5%)	2 (2.2%)	0 (0%)
Swelling	125 (83.3%)	121 (80.7%)	23 (18.4%)	89 (71.2%)	12 (9.6%)	1 (0.8%)	22 (18.2%)	85 (70.2%)	11 (9.1%)	3 (2.5%)
Pain	96 (64%)	103 (68.7%)	27 (28.1%)	67 (69.8%)	2 (2.1%)	0 (0%)	32 (31.1%)	67 (65%)	2 (1.9%)	2 (1.9%)
Tenderness	122 (81.3%)	130 (86.7%)	28 (23%)	87 (71.3%)	7 (5.7%)	0 (0%)	26 (20%)	94 (72.3%)	6 (4.6%)	4 (3.1%)
Itching	53 (35.3%)	58 (38.7%)	22 (41.5%)	27 (50.9%)	4 (7.5%)	0 (0%)	29 (50%)	26 (44.8%)	2 (3.4%)	1 (1.7%)
Other[4]	3 (2%)	3 (2%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)

[1] Missing values are not reported.
[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.
[3] Data are cumulated from up to two injection sites per patient with earliest and latest time point for any reaction provided.
[4] Two patients reported mild transient headache and one patient reported mild 'twitching'; neither could be associated with a particular product.

Table 7 shows the number of adverse experiences identified by investigators at 72 hours after injection for Studies MA-1400-01 and MA-1400-02. Some patients had multiple adverse experiences or had the same adverse experience at multiple injection sites. No adverse experiences were of severe intensity.

Table 8 presents the number of patients and per patient incidence of all adverse experiences identified by investigators at visits occurring two or more weeks after injection.

In a clinical study (31GE0003) in which safety was followed for 12 months with repeat administration of *Restylane*® at six to nine months following the initial correction, the incidence and severity of adverse experiences were similar in nature and duration to those recorded during the initial treatment sessions.

In all three studies, investigators reported the following local and systemic events that were judged unrelated to treatment and occurred at an overall incidence of less than 2%, i.e., acne; arthralgia; tooth disorders (e.g., pain, infection, abscess, fracture); dermatitis (e.g., rosacea, unspecified, contact, impetigo, herpetic); unrelated injection site reactions (e.g., desquamation, rash, anesthesia); facial palsy with co-administration of botulinum toxin; headache/migraine; nausea (with or without vomiting); syncope; gastroenteritis; upper respiratory or influenza-like illness; bronchitis; sinusitis; pharyngitis; otitis; viral infection; cystitis; diverticulitis; injuries; lacerations; back pain; rheumatoid arthritis; and various medical conditions such as chest pain, depression, pneumonia, renal stones, urinary incontinence, and uterine fibroids.

Table 9 presents the number of patients and per patient incidence and severity of injection site adverse events identified by the investigator.

Two subjects had adverse events that were severe, one subject with bilateral facial bruising and one subject with infection at the infection site. These events were considered probably or possibly related and both subjects had their events resolve in approximately 3 weeks.

Potential Adverse Events:

In postmarket surveillance of *Restylane*® in the U.S. and 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. Other events reported included herpetic eruptions, capillary disruptions including telangiectasia, injection site numbness/tingling and vasovagal reactions following injection. Additionally, delayed inflammatory reaction to *Restylane*® has been observed with swelling, redness, tenderness, induration and rarely acneform papules at the injection site with onset as long as several weeks after the initial treatment. Average duration of these effects is two weeks.

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

Clinical Trials

The safety and effectiveness of *Restylane*® in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures) were evaluated in three prospective randomized controlled clinical studies involving 430 *Restylane*® treated subjects.

Restylane® was shown to be effective when compared to cross-linked collagen and cross-linked hyaluronic acid dermal fillers with respect to the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Table 7. All Investigator-Identified Adverse Experiences (72 Hours)
Number of Events per Patient per Study

Study Term	MA-1400-01		MA-1400-02	
	Number of Events *Restylane*® (N=150)	Number of Events *Perlane*® (N=150)	Number of Events *Restylane*® (N=142)	Number of Events *Perlane*® (N=141)
Ecchymosis	9	10	48	44
Edema	4	4	6	10
Erythema	13	13	3	5
Tenderness	4	4	7	5
Pain	2	2	2	2
Hyperpigmentation	2	3	0	1
Pruritus	2	1	1	0
Papule	1	0	2	2
Burning	1	0	0	0
Hypopigmentation	1	0	0	0
Injection site scab	3	0	0	0

Table 8. Investigator-Identified Adverse Experiences (2 Weeks or More After Implantation) (Number of Patients)
***(Restylane*® v. Specified Active Controls—All Studies)**

Study Term	MA-1400-01 *Restylane*® (n=150) (%)	MA-1400-01 *Perlane*® (n=150) (%)	MA-1400-02 *Restylane*® (n=142) (%)	MA-1400-02 *Perlane*® (n=141) (%)	31GE0003 *Restylane*® (n=138) (%)	31GE0003 Zyplast® (n=138) (%)
Ecchymosis	4 (2.7%)	7 (4.6%)	14 (9.9%)	15 (10.6%)	8 (5.8%)	6 (4.3%)
Edema	0 (0%)	0 (0%)	2 (1.4%)	3 (2.1%)	11 (8.0%)	14 (10.1%)
Erythema	2 (1.3%)	2 (1.3%)	1 (0.7%)	2 (1.4%)	30 (21.7%)	37 (26.8 %)
Tenderness	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	8 (5.8%)	10 (7.2%)
Pain	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	3 (2.2%)
Papule	1 (0.7%)	0 (0%)	2 (1.4%)	1 (0.7%)	5 (3.6%)	13 (9.4%)
Pruritus	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	4 (2.9%)	8 (5.8%)
Rash	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)
Hyperpigmentation	8 (5.3%)	7 (4.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injection site scab	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin exfoliation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 9. MA-004-03 Adverse Events Reported by *Restylane*® Patients

Adverse Event	Number of Subjects with Events(%) N=75	Total Number of Events†	Severity Mild	Moderate	Severe
Swelling	18 (24%)	46	37	9	0
Bruising	14 (19%)	33	19	12	2
Pain/soreness	4 (5%)	14	12	2	0
Discoloration	3 (4%)	5	5	0	0
Infection	1 (1%)	1	0	0	1
Hardness/Nodule	2 (3%)	3	2	1	0

†Most subjects had bilateral events at either the initial injection or touch-up. Bilateral events are counted as two events.

U.S. Clinical Studies

31GE0003: Prospective, Randomized, Blinded, Controlled, Clinical Study

Design

1:1 randomized, prospective study at 6 U.S. 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.

Effectiveness was studied with 6-month follow-up. Safety was studied with 12-month follow-up.

Endpoints

Effectiveness
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.

Secondary:
Wrinkle Severity Rating Scale (WSRS) score assessed at other follow-up points by the evaluating investigator and by the subject.

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.

Number of treatment sessions to achieve optimal cosmesis.

The primary evaluation parameter was the 5-point WSRS Score. A change in WSRS=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.

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.

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.

• Gender			• Tobacco use		
Male:	9	(6.6%)	Non-smokers	118	(86.1%)
Female:	128	(93.4%)	Smokers:	19	(13.9%)
• Ethnicity			• Sun Exposure		
Caucasian:	122	(89.0%)	None:	83	(60.6%)
Black:	2	(1.5%)	Natural Sun:	52	(38.0%)
Asian:	2	(1.5%)	Artificial:	2	(1.5%)
Hispanic:	11	(8.0%)			

Effectiveness
Primary:

Based on the per patient evaluation, the WSRS scores at 6 months by the evaluating investigator demonstrated that WSRS 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 WSRS 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 WSRS) and baseline (0.01 units WSRS), for the cohort of 134 patients, there was a difference of 0.58 units of WSRS at 6 months.

Table 10. Blinded Evaluator Mean Wrinkle Severity Scores

	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

MA-1400-02: Prospective, Randomized, Blinded, Controlled Clinical Study

Design

1:1 randomized, prospective study at 17 U.S. centers, which compared the safety and effectiveness of *Restylane*® and *Perlane*® following treatment to baseline condition. Patients were randomized to either *Restylane*® or *Perlane*® treatment. A touch-up was allowed 2 weeks after initial treatment. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were unmasked.

Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.

Endpoints

Effectiveness
Primary:
The difference in effect of *Restylane*® at week 12 versus baseline condition on the visual severity of the nasolabial folds, as assessed by the Blinded Evaluator.

The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated on a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by a live evaluator blinded to treatment. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes were calculated for each treatment group. Each group was compared to its own baseline, with no comparison of *Restylane*® to *Perlane*®.

Secondary:
Wrinkle Severity Rating Scale (WSRS) assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the Blinded Evaluator, the investigator and the patient and compared to baseline score by the same evaluator. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response remaining in both nasolabial folds (NLFs).

Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.

Outcomes

Demographics:
The study enrolled 283 (i.e., 142 *Restylane*® and 141 *Perlane*®) patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females. Bilateral NLFs and oral commissures were corrected with 2.1 mL to 5.2 mL of *Restylane*.®
The greatest amount used in any patient was 8.8 mL.

Gender – Female: 266 (94%); Male: 17 (6%)

Ethnicity – White: 226 (80%); Hispanic or Latino: 31 (11%); African American: 23 (8%); Asian: 3 (1%)

Efficacy:
The results of the blinded evaluator assessment of NLF wrinkle severity for *Restylane*® and control (*Perlane*®) are presented in Table 11. In the primary effectiveness assessment at 12 weeks, 77% of the *Restylane*® and 87% of the control patients had maintained at least a 1 point improvement over baseline.

Table 11. Blinded Evaluator Wrinkle Severity Response Scores

Time point	No. of *Restylane*® Patients	No. of *Restylane*® Pts. maintaining ≥ 1 Unit Improvement of NLF on WSRS	No. of *Perlane*® Patients	No. of *Perlane*® Pts. maintaining ≥1 Unit Improvement of NLF on WSRS
6 weeks	136	113 (83%)[1]	136	121 (89%) [1]
12 weeks	140	108 (77%) [1]	141	122 (87%) [1]
24 weeks	140	103 (74%) [1]	138	87 (63%) [1]

[1] All *p* values <0.0001 based on t-test compared to baseline condition

Antibody Testing:
15/142 (10.6%) subjects displayed a pre-treatment antibody response against *Restylane*® (which was believed to be related to co-purifying *Streptococcus* capsule antigens). One subject also developed measurable increase in antibody titer after *Restylane*® injection. 7/21 (33.3%) patients with antibodies against *Restylane*® had adverse experiences at the injection site, which was similar to the local adverse event rate observed in the entire *Restylane*® population (i.e., 53/142 (37%)). No severe events were noted and the subject who developed an antibody response after *Restylane*® injection did not experience any adverse event at the injection site. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*.® Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.®

MA-1400-01: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 10 U.S. centers, which compared the safety and effectiveness of *Restylane*® and *Perlane*® following treatment to baseline condition in 150 patients with pigmented skin and predominantly African-American ethnicity. Patients were randomized to *Restylane*® or *Perlane*® treatment in a "within-patient" model of augmentation correction of bilateral nasolabial folds (NLFs) and oral commissures with one treatment assigned to one side and the other treatment to the other side. A touch-up was allowed 2 weeks after initial treatment. Patients and treating physicians were partially masked. Evaluations were performed by live investigator assessment for the primary analysis. Effectiveness was studied with 6 months follow-up. Safety was studied with 6 months follow-up.
Endpoints	Effectiveness Primary: The difference in effect of *Restylane*® at week 12 versus baseline condition on the visual severity of the NLFs. The primary study endpoint was wrinkle severity 12 weeks after optimal correction was achieved. Wrinkle severity was evaluated with a five-step validated Wrinkle Severity Rating Scale (WSRS) (i.e., none, mild, moderate, severe, extreme) by an on-site blinded evaluator. Patient success was defined as maintaining at least a one point improvement on the WSRS at 12 weeks after optimal correction was achieved. The percent of patient successes was calculated for each group. Each treatment group was compared to its own baseline, with no comparison of *Restylane*® to *Perlane*®. Secondary: Wrinkle Severity Rating Scale (WSRS) was assessed at other follow-up points (2, 6, and 24 weeks after optimal correction) by the investigator and the patient and compared to baseline score by the same evaluator. A photographic assessment of patient outcomes was also performed. Duration of effect was defined as 6 months or time point, if earlier, at which less than 50% of patients had at least a 1-grade response at both nasolabial folds. Safety assessments included: collection of patient symptoms in a 14-day diary; investigator evaluation of adverse experiences at 72 hours, and at 2, 6, 12, and 24 weeks; development of humoral or cell-mediated immunity; and the relationship of adverse experiences to injection technique.
Outcomes	**Demographics:** The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females. Gender – Female: 140/150 (93%); Male 10/150 (7%) Ethnicity – White: 2 (1.3%); Hispanic or Latino: 9 (6%); African-American: 137 (91%); American Indian: 2 (1.3%) Fitzpatrick Skin Type – I to III: 0 (0%); IV: 44 (29%); V: 68 (45%); VI: 38 (25%) **Efficacy:** The results of the live blinded evaluator assessment of wrinkle severity for *Restylane*® and control (*Perlane*®) are presented in Table 12 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 93% of the *Restylane*® treated and 92% of the *Perlane*® treated NLF maintained at least a 1 point improvement over baseline.

Table 12. Live Evaluator Wrinkle Severity Response Scores

Time point	No. of patients	No. of *Restylane*® Pts. maintaining 1 Unit Improvement on WSRS	95% *Restylane*® Confidence Interval	No. of *Perlane*® Pts. maintaining [1] 1 Unit Improvement on WSRS	95% *Perlane*® Confidence Interval
6 weeks	148	142 (96%)[1]	92–99%	140 (95%) [1]	90–99%
12 weeks	149	139 (93%) [1]	89–98%	137 (92%) [1]	87–97%
24 weeks	147	108 (73%) [1]	66–81%	104 (71%) [1]	63–77%

[1] All *p* values <0.0001 based on t-test compared to baseline condition

Antibody Testing:
9/150 (6%) subjects displayed a pre-treatment antibody response against *Restylane*® (which was believed to be related to co-purifying *Streptococcus* capsule antigens). No subjects developed a measurable increase in antibody titer after *Restylane*® injection. 1/6 (17%) patients with antibodies against *Restylane*® had adverse experiences at the injection site as compared to the local adverse event rate observed in the entire *Restylane*® population (i.e., 28/150 (18.7%)). All the adverse experiences in the patients with a humoral response against *Restylane*® were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to *Restylane*.® Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to *Restylane*.®

MA-04-003

The duration of effectiveness of *Restylane*® for correction of nasolabial folds (NLF) was evaluated in a randomized, evaluator-blinded, multi-center study. *Restylane*® was shown to have an overall duration of effectiveness of 18 months from baseline following re-treatment at 4.5 or 9 months.

MA-04-003: Randomized Clinical Study

Design	Randomized, evaluator-blinded study at 3 U.S. centers, which compared the safety and effectiveness of *Restylane*® using two re-treatment schedules. Initially *Restylane*® was injected in both nasolabial folds (NLF). Subsequently, one NLF was retreated at 4.5 months after the initial treatment. The contralateral NLF was treated with *Restylane*® and re-treated at 9 months (± 1 week). The Blinded Evaluators were blinded to the re-treatment schedule while patients and treating physicians were not. Effectiveness was studied at 18 months after the initial injection (i.e., either 9 or 13.5 months after the second treatment).
Endpoints	Effectiveness Primary: The difference in effect of *Restylane*® injected 4.5 or 9 months after the initial treatment on the visual severity of the nasolabial folds was assessed by an Evaluating Investigator at 18 months after the baseline treatment. The primary study endpoint was the proportion of subjects with at least one grade improvement in the Wrinkle Severity Rating Scale (WSRS) from baseline as assessed by the Blinded Evaluator at the 18 month visit. Secondary: The Wrinkle Severity Rating Scale (WSRS) score was assessed by the evaluating investigator at all follow-up visits prior to the 18 month visit and at all visits by subjects and independent photographic reviewers. Global Aesthetic Improvement Scale (GAIS) comparing the pre-treatment appearance at all follow-up visits up to 18 months, was determined by the treating investigator and subject. The GAIS is a 5-point scale for assessing global aesthetic improvement: "very much improved / much improved / improved / no change / worse." Safety Severity and duration of injection site reactions and adverse events were recorded.
Outcomes	**Demographics**: The study enrolled an adult population of predominately Caucasian, healthy, non-smoking females.

Number of Subjects	Age		Gender		Race		Prior Augmentation to NLF		History of Tobacco Use		History of Sun Exposure	
75	Mean ± SD	53.8 ± 8.4	Male	5 (6.7%)	White	50 (66.7%)	Yes	6 (8.0%)	No	55 (73.3%)	No	63 (84.0%)
	Median	54	Female	70 (93.3%)	Black	3 (4.0%)	No	69 (92.0%)	Yes	20 (26.7%)	Yes	12 (16.0%)
	Minimum	26			Hispanic	22 (29.3%)						
	Maximum	73										

Number of Subjects enrolled and observed at 4.5, 9, 12, 15 and 18 months								
	SCR/TRT	Touch-up	Wk2	M 4.5	M9	M12	M15	M18
Enrolled	75	-	75	75	75	75	75	75
Withdrew Consent (total)	0	-	1	5	6	6	6	7
Lost to Follow-up	0	-	0	2	4	4	4	4
Missed Visit	0	-	2	1	0	1	1	1
Actual	75	44	72	67	65	64	64	64

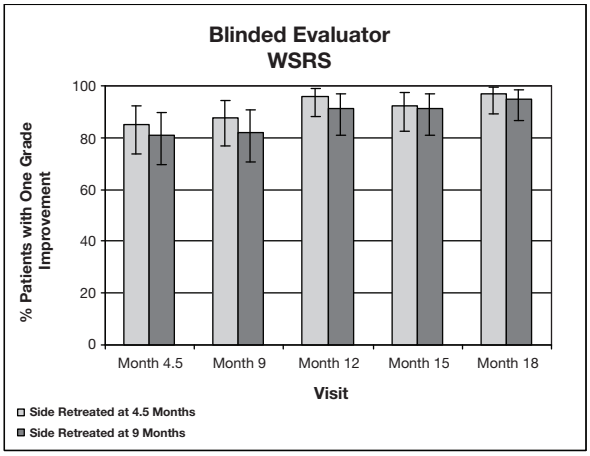
Volume (mL) of *Restylane*® Treatment Used by Visit

Visit	Side Assigned to Re-treatment at 4.5 Months	Side Assigned to Re-treatment at 9 Months
Baseline		
N	75	75
Mean ± SD	1.1 ± 0.61	1.1 ± 0.56
Median	1.0	1.0
Minimum	0.1	0.2
Maximum	2.5	2.5
Touch-up Visit		
N	44	44
Mean ± SD	0.5 ± 0.22	0.5 ± 0.21
Median	0.5	0.5
Minimum	0.2	0.2
Maximum	1.0	1.0
Re-treatment Visit (4.5 Months/9 months)		
N	67	63
Mean ± SD	0.7 ± 0.33	0.7 ± 0.36
Median	0.8	0.6
Minimum	0.2	0.1
Maximum	1.8	2.0

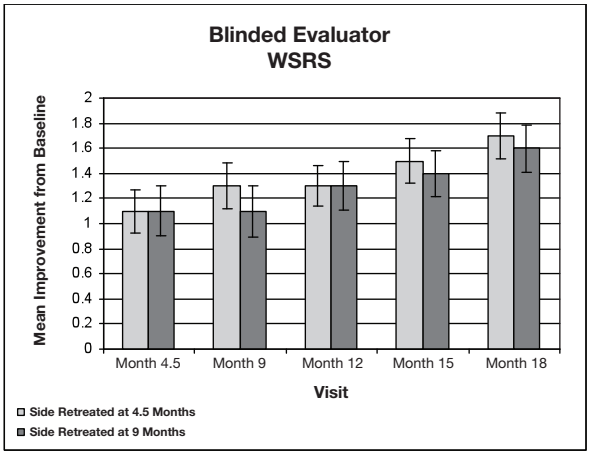
MA-04-003: Randomized Clinical Study

Effectiveness

The results of the blinded evaluator assessment of NLF wrinkle severity for subjects treated at baseline, 4.5 or 9 months is presented in the Figure below for subject outcomes at 4.5, 9, 12, 15 and 18 months after initial treatment.



At 18 months after the initial treatment, the blinded evaluator determined that 97% of the NLFs retreated at 4.5 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.7 units. At 18 months after the initial treatment, the blinded evaluator determined that 95% of the NLFs retreated at 9 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.6 units.



HOW SUPPLIED

Restylane® is supplied in a disposable glass syringe with a Luer-Lok® fitting. *Restylane*® is co-packed with sterilized needle(s) as indicated on the carton, either 30 G x ½" or 29 G x ½".

A patient record label is a part of the syringe label. Remove it by pulling the flap marked with three small arrows. 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 and needle gauge is as stated on the syringe label and on the carton.

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. Protect from sunlight. Refrigeration is not required.

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.

℞ only

U.S. PATENT 5,827,937

Manufactured for
Medicis Aesthetics Inc.
7720 N. Dobson Road
Scottsdale, AZ 85256
U.S.A.
Phone: 1-866-222-1480

Manufactured by
Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

DIRECTIONS FOR ASSEMBLY

ASSEMBLY OF 30 G NEEDLE TO SYRINGE

For safe use of *Restylane*,® it is important that the needle is properly assembled. Improper assembly may result in separation of the needle and syringe during implantation.

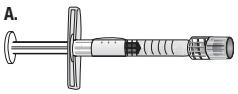
See pictures A through E.

1. Unscrew the tip cap (B) of the syringe carefully.
2. Grasp the narrow part of the needle shield loosely; mount the needle on the Luer-Lok® (C) by turning it clockwise until you feel counterpressure.
3. Grasp the wider part of the needle shield firmly (D).
4. Press and turn the needle shield 90° (a quarter turn).

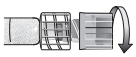
4a. The quarter turn is necessary to lock the needle onto the syringe.

5. Remove the patient record label marked with three small arrows (E) and attach to patient chart.
6. Pull off the needle shield.

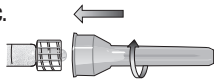
A.



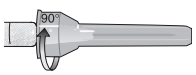
B.



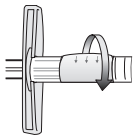
C.



D.

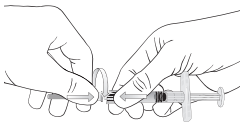


E.



ASSEMBLY OF 29 G NEEDLE TO SYRINGE

Use the thumb and forefinger to hold firmly around both the glass syringe barrel and the Luer-Lok® adapter. Grasp the needle shield with the other hand. To facilitate proper assembly, both push and rotate firmly.



PRE-TREATMENT GUIDELINES

Prior to treatment, the patient should avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements. These agents may increase bruising and bleeding at the injection site.

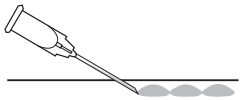
TREATMENT PROCEDURE

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 appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
3. The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
4. Sterile gloves are recommended while injecting *Restylane*.®
5. Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
6. *Restylane*® is administered using a thin gauge needle (30 G x ½" or 29 G x ½"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. *Restylane*® should be injected into the mid to deep dermis. If *Restylane*® is injected too superficially this may result in visible lumps and/or bluish discoloration.
7. Inject *Restylane*® applying even pressure on the plunger rod. 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.
8. Only correct to 100% of the desired volume effect. Do not overcorrect. With cutaneous 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.
9. Typical usage for each treatment session is specific to the site as well as wrinkle severity. In a prospective study of midface wrinkle correction, the median total dose was 3.0 mL. Based on U.S. clinical studies, the maximum recommended dose per treatment is 6.0 mL.

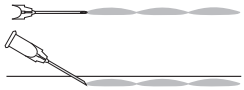
INJECTION TECHNIQUES

1. *Restylane*® can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
2. **Serial puncture** (F) involves multiple, closely spaced injections along wrinkles or folds. Although serial puncture allows precise placement of the filler, it produces multiple puncture wounds that may be undesirable to some patients.
3. **Linear threading** (G) is accomplished by fully inserting the needle into the middle of the wrinkle or fold and injecting the filler along the track as a "thread." Although threading is most commonly practiced after the needle has been fully inserted and is being withdrawn, it can also be performed while advancing the needle ("push-ahead" technique).
4. Serial threading is a technique that utilizes elements of both approaches.
5. **Cross-hatching** (H) consists of a series of parallel linear threads injected at intervals of five to ten mm followed by a new series of threads injected at right angles to the first set to form a grid. This technique is particularly useful in facial contouring when coverage of the treatment region needs to be maximized.
6. **Note! The correct injection technique is crucial for the final result of the treatment.** Dissection of the sub-epidermal plane with lateral movement of the needle, rapid flows (>0.3 mL/min), rapid injection or high volumes may result in an increase in short-term episodes of bruising, swelling, redness, pain, or tenderness at the injection site.

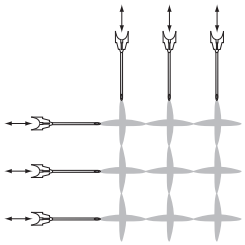
F. Serial Puncture



G. Linear Threading



H. Cross-hatching



7. 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.
8. 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.
9. If the wrinkle needs further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane*® may be necessary to achieve the desired correction.
10. If the treated area is swollen directly after the injection, an ice pack can be applied on the site for a short period. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
11. Patients may have mild to moderate injection site reactions, which typically resolve in a few days.

STERILE NEEDLE(S)

- 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 reshield used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.
- *Restylane*® is provided with a needle that does not contain engineered injury protection. Administration of *Restylane*® requires direct visualization and complete and gradual insertion of the needle making engineered protections infeasible. Care should be taken to avoid sharps exposure by proper environmental controls.

Ordering Information

Medicis Aesthetics Inc. and its distributor, McKesson Specialty, are your only sources for FDA-approved *Restylane*.® Purchasing from any other agent is illegal.

To order call 877-520-0500.

* NOTE: This printer-friendly version has been modified to print on letter paper. The formatting, size, and location of text, diagrams, and tables may be different from the package insert.

Revised: December 2008
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