



Restylane-L™

Injectable Gel with 0.3% Lidocaine

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

Description
Restylane-L is a gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically crosslinked with BDE, stabilized and suspended in phosphate buffered saline at pH=7 and concentration of 20 mg/mL with 0.3% lidocaine.

Indication
Restylane-L 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-L is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

Restylane-L contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.

Restylane-L is contraindicated for patients with bleeding disorders.

Restylane-L is contraindicated for implantation in anatomical spaces other than the dermis.

Restylane-L should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.

Warnings
Defer use of *Restylane-L* 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-L* 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 events section for details.

Restylane-L 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-L 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-L* for the treatment of anatomic regions other than nasolabial folds has not been established in controlled clinical studies.

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

The safety and efficacy of *Restylane-L* for lip augmentation has not been established.

The safety of *Restylane-L* 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-L*. Keloid formation was not observed in studies involving 430 patients (including 151 African-American 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. In study MA-1100-01 with *Restylane* and *Restylane-L*, there were 53.3% (32/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of keloid formation.

Restylane injection may cause hyperpigmentation at the injection site. In a clinical study of 150 patients 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. In study MA-1100-01 with *Restylane* and *Restylane-L*, there were 53.3% (32/60) of patients with Fitzpatrick Skin Types IV, V, and VI and no reports of hyperpigmentation.

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

Bruising or bleeding may occur at *Restylane-L* injection sites. *Restylane-L* 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-L* 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-L*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane-L* is administered before the skin has healed completely after such a procedure.

Injection of *Restylane-L* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.

Restylane-L 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 Medtronic 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-L should not be mixed with other products before implantation of the device.

Adverse Experiences
There were five U.S. studies that reported adverse events.

In three U.S. studies (i.e., MA-1400-01, 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 9. In study 31GE0003, 138 patients at 6 centers received *Restylane* injections in one 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 10 presents all investigator-identified adverse events 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 11. 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.

In a fifth U.S. study (MA-1100-001) 60 patients at three centers randomly received *Restylane-L* injections on one side of the face and *Restylane* injections on the other side of the face. The adverse events reported in patient diaries during 14 days after treatment are presented in Tables 7 and 8. The physician recorded adverse events identified in study MA-1100-001 at 14 days after injection are presented in Table 12.

Table 9 shows the number of adverse events identified by investigators at 72 hours after injection for Studies MA-1400-01 and MA-1400-02. Some patients had multiple adverse events or had the same adverse event at multiple injection sites. No adverse events were of severe intensity.

Table 10 presents the number of patients and per patient incidence of all adverse events 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 events 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 11 presents the number of patients and per patient incidence and severity of injection site adverse events identified by the investigator.

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

Table 12 shows the number of adverse events identified by investigators during Day 1 through Day 14 after injection in Study MA-1100-01.

Some patients had multiple adverse events or had the same adverse events at bilateral injection sites. No adverse events were of severe intensity. Patients were queried on adverse events on the day of injection and at the Day 14 visit.

Study MA-1100-001, included 52 subjects who had no prior cosmetic treatment and 8 subjects who had prior dermal filler treatment. There were no statistical differences in the proportion of subjects with adverse events who had prior treatment and those with no prior treatment.

Post Marketing Surveillance:
The following adverse events were received from post-marketing surveillance for *Restylane* and *Perlane* in the U.S. and other countries: presumptive bacterial infections, inflammatory adverse events, necrosis, injection site numbness/tingling, and vasovagal reactions. Reported treatments have included systemic steroids, systemic antibiotics, and intravenous administrations of medications. Additionally, delayed inflammatory reaction to *Restylane* has been observed with swelling, redness, tenderness, induration and rarely acneiform papules at the injection site with onset as long as several weeks after the initial treatment. Average duration of these effects is two weeks.

Implant and injection site reactions, mostly non-serious events, have also been reported. These include: discoloration, bruising, swelling, redness, formation of cysts, pain, scarring and ischemia. Most instances of discoloration including hyperpigmentation, sometimes described as a blue or brown color and ranging from mild to severe, have occurred within the same day as treatment but also occurred up to 6 months post treatment. These events typically resolve within a few days but with some infrequent instances lasting up to 18 months. Implant and/or injection site bruising, swelling, erythema and pain generally occurred on the same day as treatment usually resolving within 1 to 4 weeks. Some occurrences have persisted for up to 6 months. Severity for these events is generally mild to moderate although some cases have been severe. Mild to moderate mass formations (typically described as lumps or bumps) have also been seen ranging in onset from 1 day to 6 months post implantation. Rarely, events of this type have been observed up to 13 months. These events usually resolved within 1 to 5 months. Mild to moderate scarring was rarely observed. Onset of symptoms ranged from immediate post treatment up to 1 year following implantation. Symptom resolution was approximately 3 weeks with 1 instance lasting up to 3 years. Most ischemic events have occurred immediately following implantation and ranged in severity from moderate to severe. Events were resolving as early as 2 days and up to 9 weeks post treatment.

Symptoms associated with herpetic eruptions which included swelling, pain, whiteheads, vesicles and erythema have been reported and commonly occurred within 2 days to 1 month following implantation. Severity ranged from mild to moderate and resolution of symptoms ranged from 1 to 15 weeks.

Telangiectasias and capillary disorders, commonly characterized as broken capillaries, have been reported and occurred with an onset of 1 day to 7 weeks. Most events ranged in severity from mild to moderate with a few severe instances. Duration of events ranged from 2 weeks up to 13 months.

Very rarely, instances of moderate to severe biopsy confirmed granuloma were observed. Onset ranged from 3 weeks to 4 months with resolution between 6 weeks to 11 months.

Events of mild to moderate hypoesthesia have occurred ranging in onset from 1 day to 1 week. Duration and resolution occurred between 1 day and 10 weeks.

Serious adverse events have been rarely reported. The most commonly reported serious adverse events (by MedDRA Preferred Term) were hypersensitivity, and implant and/or injection site swelling, ischemia and discoloration. Of these infrequently reported serious events, only one adverse event has occurred in a frequency of 5 or greater:

- Hypersensitivity reactions ranging from moderate to severe mostly occurred within 1 to 2 days of implantation and up to 3 weeks. Reported symptoms included swelling; itching on chest and back; puffy, burning, watery, and itchy eyes; and shortness of breath. Treatments included steroids, diphenhydramine, unspecified intravenous medication, oxygen and various creams. An evaluation of patients who reported potential hypersensitivity reactions did not demonstrate any evidence of IgE or cell-mediated immunologic reactions specifically directed at hyaluronic acid. Most hypersensitivity events resolved within 1 to 14 days with or without treatment.

Adverse reactions should be reported to Medtronic 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 patients.

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.

The safety and pain reduction effect of *Restylane-L* in the treatment of facial folds and wrinkles (nasolabial folds) was evaluated in a prospective randomized controlled clinical study involving 60 patients. The addition of lidocaine to *Restylane-L* resulted in a statistically significant reduction in the pain experienced by the patients. The study also showed that the safety profile of *Restylane-L* was consistent with *Restylane*.

	<i>Restylane</i> side				<i>Zyplast</i> 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 (84.9%)	117 (84.9%)	117 (84.9%)	56 (40.6%)	54 (39.1%)	7 (5.1%)	17 (12.3%)	72 (52.2%)	37 (26.8%)	6 (5.6%)
Swelling	120 (87.9%)	120 (87.9%)	141 (103.1%)	54 (39.1%)	61 (44.2%)	5 (3.6%)	32 (23.2%)	66 (47.7%)	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.

	<i>Restylane</i> side		<i>Zyplast</i> side							
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days	Number of days						
			1	2-7	8-13	14	1	2-7	8-13	14
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	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 (84.9%)	117 (84.9%)	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 (87.9%)	120 (87.9%)	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%)

	<i>Perlane</i>		<i>Restylane</i> Patients				<i>Perlane</i> Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable ¹ n (%)	Affected Daily Activity ² n (%)	Disabling ³ n (%)	None n (%)	Tolerable ¹ n (%)	Affected Daily Activity ² n (%)	Disabling ³ n (%)
Bruising	111 (82.2%)	122 (86.5%)	28 (20.1%)	82 (59.9%)	28 (20.1%)	1 (0.7%)	17 (12.2%)	97 (69.8%)	24 (17.3%)	1 (0.7%)
Redness	114 (83.7%)	118 (85.7%)	25 (18%)	96 (69.1%)	17 (12.2%)	1 (0.7%)	105 (75.5%)	105 (75.5%)	12 (8.6%)	1 (0.7%)
Swelling	127 (93.4%)	128 (93.8%)	12 (8.6%)	102 (73.4%)	23 (16.5%)	2 (1.4%)	117 (77.9%)	107 (77.1%)	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 (18.1%)	96 (69.1%)	18 (12.9%)	0 (0%)
Tenderness	123 (89.6%)	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 ⁴	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.

	<i>Perlane</i>		<i>Restylane</i> Patients				<i>Perlane</i> Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	Number of days ¹	Number of days ¹	Number of days ¹	Number of days ¹	Number of days ¹	Number of days ¹	Number of days ¹	Number of days ¹
			1	2-7	8-13	14	1	2-7	8-13	14
			n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bruising	111 (82.2%)	122 (86.5%)	9 (6.4%)	69 (50.0%)	30 (21.7%)	3 (2.2%)	6 (4.4%)	81 (58.4%)	28 (20.3%)	7 (5.1%)
Redness	114 (83.7%)	118 (85.7%)	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 (93.4%)	128 (93.8%)	12 (8.4%)	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 (89.6%)	130 (92.2%)	21 (17.1%)	92 (74.8%)	9 (7.3%)	1 (0.8%)	24 (19.5%)	89 (68.3%)	16 (12.3%)	1 (0.8%)
Itching	67 (47.2%)	45 (31.9%)	22 (23.9%)	38 (56.7%)	1 (1.3%)	1 (1.3%)	19 (22.2%)	23 (33.3%)	3 (4.3%)	0 (0%)
Other ²	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.

	<i>Restylane</i>		<i>Restylane</i> Patients				<i>Perlane</i> Patients			
	Total patients reporting symptoms n (%)	Total patients reporting symptoms n (%)	None n (%)	Tolerable ¹ n (%)	Affected Daily Activity ² n (%)	Disabling ³ n (%)	None n (%)	Tolerable ¹ n (%)	Affected Daily Activity ² n (%)	Disabling ³ n (%)
Bruising	70 (46.7%)	74 (49.3%)	79 (52%)	64 (44.2%)	4 (2.7%)	0 (0%)	75 (50.3%)	67 (45%)	7 (4.7%)	0 (0%)
Redness	87 (56%)	92 (61.3%)	82 (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 (12.6%)	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 (36.7%)	4 (2.7%)	0 (0%)
Other ⁴	3 (2%)	3 (2%)	NA	3 (100%)	0 (0%)	0 (0%)	NA	3 (100%)	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 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 "itching"; neither could be associated with a particular product.

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 re-treated 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
Effectiveness was studied at 18 months after the initial injection (i.e., either 9 or 13.5 months after the second treatment).

Endpoints
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 patients 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 patients and independent photographic reviews. 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 patient. 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.

Demographics:
The study enrolled an adult population of predominantly Caucasian, healthy, non-smoking females.

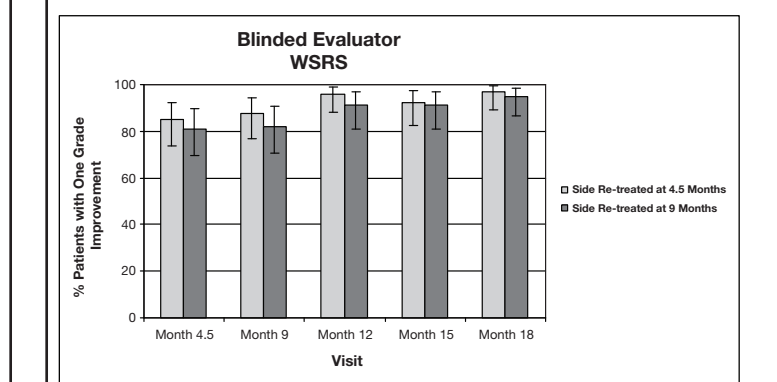
Number of Patients	Age	Gender	Race	Prior Augmentation to NLF		History of Tobacco Use		History of Sun Exposure	
				Yes	No	Yes	No	Yes	No
75	Mean ± SD 53.8 ± 8.4	Male 5 (6.7%)	White 50 (66.7%)	6 (8.0%)	69 (92.0%)	55 (73.3%)	20 (26.7%)	63 (84.0%)	12 (16.0%)
	Median 54	Female 70 (93.3%)	Black 3 (4.0%)	No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

	Number of Patients enrolled and observed at 4.5, 9, 12, 15 and 18 months							
	SCR/TRT	Touch-up	Wk2	M4.5	M9	M12	M15	M18
Enrolled	75	-	75	75	75	75	75	75
Withdraw 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

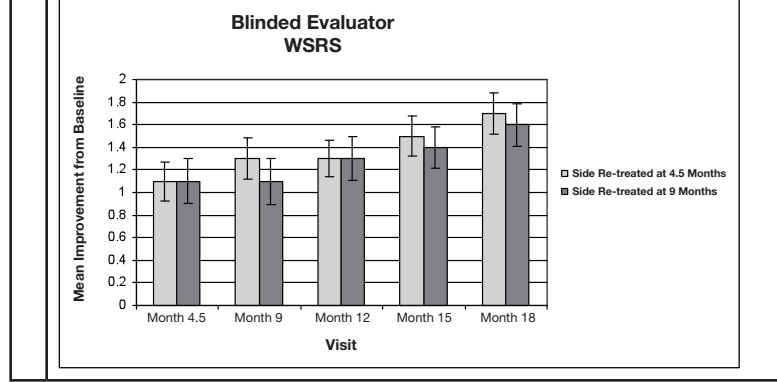
Volume (mL) of *Restylane* Treatment Used by Visit

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

Effectiveness
The results of the blinded evaluator assessment of NLF wrinkle severity for patients treated at baseline, 4.5 or 9 months is presented in the Figure below for patient 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 re-treated 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 re-treated at 9 months displayed at least 1 WSRS grade improvement over baseline, with a mean change in wrinkle severity score of 1.6 units.



MA-1100-001: Randomized, Blinded, Controlled Clinical Study

Design
1:1 randomized, prospective study at 3 U.S. centers, which compared the safety, tolerability, and pain reduction of *Restylane-L* compared to *Restylane* in 60 patients. Patients were randomized to *Restylane-L* or *Restylane* treatment in a "within-patient" model of bilateral nasolabial folds (NLFs) correction, with one treatment assigned to one side and the other treatment to the remaining side. Patients and treating physicians were blinded; evaluating physicians were independent and blinded. The study included 53.3% of patients with darker skin types based on classification of Fitzpatrick Skin Types IV, V, or VI (35% Skin Type IV and 18.3% Skin Type V or VI).

Pain was assessed by each patient for each treatment site independently on the Visual Analog Scale (VAS) at the end of injection and at 15-minute intervals for 60 minutes post-treatment. Patient assessment of appearance using the Global Aesthetic Improvement Scale (GAIS) (very much improved / much improved / improved / no change / worse) was performed at the Day 14 visit. Safety was studied with 14-day follow-up.

Endpoints
Primary:
The proportion of patients that had a within-patient difference in the VAS (*Restylane-L* – *Restylane-L*) of at least 10 mm at injection together with a 95% confidence interval. The objective was to show that the confidence interval lay above 50%.

Secondary:
The proportion of patients that had a within-patient difference in VAS of at least 10 mm at post-injection time points (15, 30, 45 and 60 minutes after injection) together with a 95% confidence interval, the mean VAS by treatment and within-patient difference in VAS at each time point, the comparison of VAS between *Restylane-L* and *Restylane*, at each time point, and patient assessment on GAIS by treatment.

Safety assessments included: collection of patient symptoms in a 14-day diary and investigator evaluation of adverse events at 14 days.

Demographics:
The study enrolled 60 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females.

Gender – Female: 58 (96.7%); Male: 2 (3.3%)

Ethnicity – White: 34 (56.7%); Hispanic or Latino: 21 (35.0%); African American: 3 (5.0%); Asian: 1 (1.7%); Other: 1 (1.7%)

Fitzpatrick Skin Type- Type I-III: 28 (46.7 %); Type IV: 21 (35.0%); Type V and VI: 11 (18.3%)

Volume:
The mean volume of *Restylane-L* per wrinkle was 1.24 mL. The mean volume of *Restylane* per wrinkle was 1.23 mL.

Volume Injected per Wrinkle (mL) (Study MA-1100-001)						
Treatment	n	Mean	Std	Min	Median	Max
<i>Restylane</i> per NLF	60	1.23	0.55	0.60	1.00	3.00
Difference within patient**	60	-0.01	0.18	-0.50	0.00	0.40

Outcomes
Primary: The primary efficacy analysis for pain reduction showed that 71.7% of patients had a within-patient difference in VAS (*Restylane* minus *Restylane-L*) of at least 10 mm at the time of injection. The primary objective was met, since statistically more than 50% of patients had at least 10 mm lower score on VAS on the side treated with *Restylane-L* (confidence interval was 58.6 to 82.5). At 15 minutes post injection, 46.7% still had a within-patient difference in VAS of at least 10 mm.

Treatment Difference (Δ) in VAS (<i>Restylane</i> Side – <i>Restylane-L</i> Side) — ITT Population (Study MA-1100-001)					
Time point	No. of patients with assessments**	Number of patients with Δ > 10 mm			
		n	%	95% LCL	95% UCL
Treatment*	60	43	71.7	58.6	82.5
15 Minutes	60	28	46.7	33.7	60.0
30 Minutes	60	17	28.3	17.5	41.4
45 Minutes	60	10	16.7	8.3	28.5
60 Minutes	60	4	6.7	1.8	16.2

* Primary endpoint
** Denominator (N), % = 100*(n/N). UCL=upper confidence limit; LCL=lower confidence limit

Secondary: Both pain scores decreased over time, but the mean within-patient difference on VAS (*Restylane* – *Restylane-L*) was statistically significantly larger than zero at all time points (at injection and at 15, 30, 45 and 60 minutes post injection).

Patients' Mean VAS Assessments of Pain by Time Point (Study MA-1100-001)				
Time point	VAS pain by treatment (mm)		VAS difference (mm)**	p-value**
	<i>Restylane-L</i>	<i>Restylane</i>		
Treatment*	14.7	44.9	30.3	<0.001
15 Minutes	6.1	23.2	17.2	<0.001
30 Minutes	2.5	11.7	9.2	<0.001
45 Minutes	1.4	7.0	5.6	<0.001
60 Minutes	1.0	3.2	2.2	<0.001

* Within-patient difference (*Restylane* side – *Restylane-L* side). ** One-sample t-test

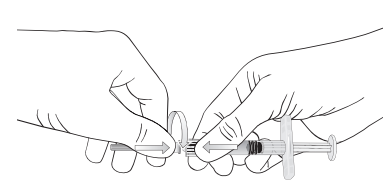
At Day 14, subjects showed improvement from baseline: 100% on the *Restylane-L* side of the face and 98.3% on the *Restylane* side of the face.

Global Aesthetic Improvement Scale (GAIS) Evaluation at the Day 14 Visit (Study MA-1100-001)				
Category	GAIS			
	<i>Restylane-L</i>		<i>Restylane</i>	
	n	%	n	%
Very Much Improved (4)	17	28.3	18	30.0
Much Improved (3)	29	48.3	29	48.3
Improved (2)	14	23.3	12	20.0
No Change (1)	-	0.0	1	1.7
Worse (0)	-	0.0	-	0.0

DIRECTIONS FOR ASSEMBLY
ASSEMBLY OF 30 G NEEDLE TO SYRINGE
For safe use of *Restylane-L*, 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.
- Unscrew the tip cap (B) of the syringe carefully.
- 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.
- Grasp the wider part of the needle shield firmly (D).
- Press and turn the needle shield 90° (a quarter turn).
- The quarter turn is necessary to lock the needle onto the syringe.
- Remove the patient record label marked with three small arrows (E) and attach to patient chart.
- Pull off the needle shield.

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.

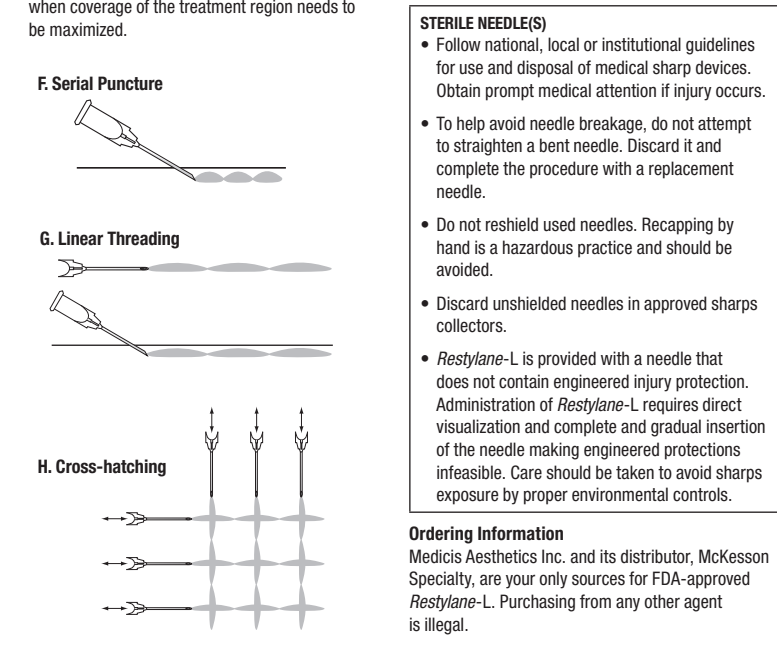


PRE-TREATMENT GUIDELINES
Prior to treatment, the patient should avoid taking aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements. These agents may increase bruising and bleeding at the injection site.

- TREATMENT PROCEDURE**
- It is necessary to counsel the patient and discuss the appropriate indication, risks, benefits and expected responses to the *Restylane-L* treatment. Advise the patient of the necessary precautions before commencing the procedure.
 - Assess the patient's need for appropriate anesthetic treatment for managing comfort, i.e., topical anesthetic, local or nerve block.
 - 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.
 - Sterile gloves are recommended while injecting *Restylane-L*.
 - Before injecting, press rod carefully until a small droplet is visible at the tip of the needle.
 - Restylane-L* is administered using a thin gauge needle (30 G x 1/2" or 29 G x 1/2"). The needle is inserted at an approximate angle of 30° parallel to the length of the wrinkle or fold. *Restylane-L* should be injected into the mid to deep dermis. If *Restylane-L* is injected too superficially this may result in visible lumps and/or bluish discoloration.
 - Inject *Restylane-L* 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.
 - 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.

- 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.
- 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.

- INJECTION TECHNIQUES**
- Restylane-L* can be injected by a number of different techniques that depend on the treating physician's experience and preference, and patient characteristics.
 - 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.
 - 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).
 - Serial threading is a technique that utilizes elements of both approaches.
 - 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.



- 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.
- 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.
- If the wrinkle needs further treatment, the same procedure should be repeated until a satisfactory result is obtained. Additional treatment with *Restylane-L* may be necessary to achieve the desired correction.
- 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.
- 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 resharpen used needles. Recapping by hand is a hazardous practice and should be avoided.
- Discard unshielded needles in approved sharps collectors.
- Restylane-L* is provided with a needle that does not contain engineered injury protection. Administration of *Restylane-L* 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-L*. Purchasing from any other agent is illegal.

To order call 877-520-0500.

