

PERLANE[®]

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

Description

PERLANE[®] is a sterile gel of hyaluronic acid generated by *Streptococcus* species of bacteria, chemically cross-linked with BDDE, stabilized and suspended in phosphate buffered saline at pH = 7 and concentration of 20 mg/mL. The largest fraction of gel particles size is between 940 and 1090 microns.

Indication

PERLANE[®] is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds.

Contraindications

- PERLANE[®] is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- PERLANE[®] contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- PERLANE[®] is contraindicated for patients with bleeding disorders.
- PERLANE[®] is contraindicated for implantation in anatomical spaces other than the dermis or superficial layer of the subcutis.

Warnings

- Defer use of PERLANE[®] 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 PERLANE[®] 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 reactions section for details.
- PERLANE[®] 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

- PERLANE[®] 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 6.0 mL per patient per treatment. The safety of injecting greater amounts has not been established.
- The safety or effectiveness of PERLANE[®] for the treatment of anatomic regions other than nasolabial folds has not been established in controlled clinical studies.
- Long term safety and effectiveness of PERLANE[®] beyond one year have not been investigated in clinical trials.
- As with all transcutaneous procedures, PERLANE[®] implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety and efficacy of PERLANE[®] for lip augmentation has not been established.
- The safety of PERLANE[®] 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 PERLANE[®]. Keloid formation was not observed in studies involving 509 patients (including 150 African-Americans and 25 other patients of Fitzpatrick Skin Types IV, V and VI). For additional information please refer to Studies MA-1400-02, MA-1400-01, 31GE0002, and 31GE0101 in the Clinical Trials Section.
- PERLANE[®] 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 6% (9/150). 50% of these events lasted up to six weeks after initial implantation.
- PERLANE[®] should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at PERLANE[®] injection sites. PERLANE[®] 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 PERLANE® 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 PERLANE®, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if PERLANE® is administered before the skin has healed completely after such a procedure.
- Injection of PERLANE® into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- PERLANE® 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 also 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.
- PERLANE® should not be mixed with other products before implantation of the device.

Adverse Experiences

In two U.S. studies (i.e., Study MA-1400-01 and Study MA-1400-02) involving 433 patients at 25 centers, the adverse outcomes reported in patient diaries during 14 days after treatment are presented in Tables 1-4. The physician diagnosed adverse events identified in these studies at 72 hours after injection are presented in Table 5. In Study MA-1400-01, 150 patients were injected with PERLANE® on one side of the face and RESTYLANE® on the other side of the face. In study MA-1400-02, 283 patients were randomized to receive either PERLANE® or RESTYLANE® injection on both sides of the face. Table 6 presents all investigator-identified adverse experiences recorded at study visits 2 weeks or more after injection in studies MA-1400-01, MA-1400-02, 31GE 0101 and 31GE 0002. In Study 31GE 0101, 150 Canadian patients were injected with both PERLANE® and Hylaform®. In Study 31GE002, 68 Swedish patients underwent both PERLANE® and Zyplast® injections.

Table 1. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-02)¹

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

¹Missing values are not reported.

²Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.

³Two 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 2. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-02)¹

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

¹Missing values are not reported.

²Data are cumulated from up to four injection sites per patient with earliest and latest timepoint for any reaction provided.

³Two 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 3. Maximum Intensity of Symptoms after Initial Treatment, Patient Diary (Study MA-1400-01)^{1,2}

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

¹Missing values are not reported.

²Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

³Prospective definitions for: tolerable, affected daily activity and disabling were not provided in the diary or protocol.

⁴Two patients reported mild transient headache and one patient reported mild 'twitching'; neither could be associated with a particular product.

Table 4. Duration of Adverse Events after Initial Treatment, Patient Diary (Study MA-1400-01)^{1,2}

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

¹Missing values are not reported.

²Events are reported as local events; because of the design (split-face) of the study, causality of the systemic adverse events cannot be assigned.

³Data are cumulated from up to two injection sites per patient with earliest and latest timepoint for any reaction provided.

⁴Two patients reported mild transient headache and one patient reported mild 'twitching'; neither could be associated with a particular product.

Table 5 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 5. 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 PERLANE® (N=150)	Number of Events RESTYLANE® (N=150)	Number of Events PERLANE® (N=141)	Number of Events RESTYLANE® (N=142)
Ecchymosis	10	9	44	48
Edema	4	4	10	6
Erythema	13	13	5	3
Tenderness	4	4	5	7
Pain	2	2	2	2
Hyperpigmentation	3	2	1	0
Pruritus	1	2	0	1
Papule	0	1	2	2
Burning	0	1	0	0
Hypopigmentation	0	1	0	0
Injection site scab	0	3	0	0

Table 6 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.

Table 6. Investigator-Identified Adverse Experiences (2 Weeks or More After Implantation)								
(Number of Patients)								
(PERLANE [®] v. Specified Active Controls – All Studies)								
Study Term	MA-1400-01 PERLANE [®] (n=150) (%)	MA-1400-01 RESTYLANE [®] (n=150) (%)	MA-1400-02 PERLANE [®] (n=141) (%)	MA-1400-02 RESTYLANE [®] (n=142) (%)	31GE 0101 PERLANE [®] (n=150) (%)	31GE 0101 Hylaform [®] (n=150) (%)	31GE 0002 PERLANE [®] (n=68) (%)	31GE 0002 Zyplast [®] (n=68) (%)
Ecchymosis	7 (4.6%)	4 (2.7%)	15 (10.6%)	14 (9.9%)	6 (4.0%)	2 (1.3%)	0 (0%)	0 (0%)
Edema	0 (0%)	0 (0%)	3 (2.1%)	2 (1.4%)	14 (9.3%)	6 (4.0%)	4 (5.9%)	9 (13.2%)
Erythema	2 (1.3%)	2 (1.3%)	2 (1.4%)	1 (0.7%)	13 (8.7%)	8 (5.3%)	6 (8.8%)	8 (11.8%)
Tenderness	1 (0.7%)	0 (0%)	1 (0.7%)	0 (0%)	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)
Pain	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	13 (8.7%)	3 (2.0%)	0 (0%)	2 (2.9%)
Papule	0 (0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)	11 (7.3%)	1 (0.7%)	1 (1.5%)	6 (8.8%)
Pruritus	0 (0%)	1 (0.7%)	0 (0%)	1 (0.7%)	2 (1.3%)	3 (2.0%)	3 (4.4%)	5 (7.4%)
Rash	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)
Hyperpigmentation	7 (4.7%)	8 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injection site scab	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin exfoliation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)

In two studies (*i.e.*, 31GE0101 and 31GE 0002) with repeat administration of PERLANE[®] at 6 - 9 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 four studies, investigators reported the following local and systemic events that were judged unrelated to treatment and occurred at an incidence of less than 1%, *i.e.*, acne; 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, renal stones, and uterine fibroids.

Potential Adverse Events:

In postmarket surveillance of Restylane in the U.S. and both Restylane and Perlane 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, 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.

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

Clinical Trials

The safety and effectiveness of PERLANE® in the treatment of facial folds and wrinkles (nasolabial folds and oral commissures) were evaluated in four prospective randomized controlled clinical studies involving 509 PERLANE® treated subjects.

PERLANE® 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.

U.S. Clinical Studies

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

Design	1:1 randomized, prospective study at 17 US centers, which compared the safety and effectiveness of PERLANE® and RESTYLANE® following treatment to baseline condition. Patients were randomized to either PERLANE® or RESTYLANE® 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 month follow-up. Safety was studied with 6 months follow-up.
Endpoints	Effectiveness Primary: The difference in effect of PERLANE® 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 Perlane to Restylane.

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 defined as 6 months or timepoint, 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., 141 Perlane and 142 Restylane) patients with moderate to severe NLF wrinkles. The patients were predominantly healthy ethnically diverse females. Bilateral NLFs and oral commissures were corrected in most patients with 1.9 mL to 4.6 mL of Perlane. The greatest amount used in any patient was 9.0 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 Perlane and control (Restylane) are presented in Table 7. In the primary effectiveness assessment at 12 weeks, 87% of the Perlane and 77% of the control patients had maintained at least a 1 point improvement over baseline.

Table 7: Blinded Evaluator Wrinkle Severity Response Scores

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

All p values <0.0001 based on t-test compared to baseline condition

	<p>Antibody Testing: 15/141 (10.6%) subjects displayed a pre-treatment antibody response against PERLANE[®] (which was believed to be related to co-purifying <i>Streptococcus</i> capsule antigens). One subject also developed a measurable increase in antibody titer after PERLANE[®] injection. 4/16 (27%) patients with antibodies against PERLANE[®] had adverse experiences at the injection site, which was similar to the local adverse event rate observed in the entire PERLANE[®] population (i.e., 49/141 (35%)). With the exception of one moderate bruising event, all the adverse experiences in the patients with a humoral response against PERLANE[®] were mild in severity. No severe events were noted and the subject who developed an antibody response after PERLANE[®] injection did not experience any adverse event at the injection site. Immediate type skin testing demonstrated that no patient developed IgE to PERLANE[®]. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to PERLANE[®].</p>
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MA-1400-01: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	<p>1:1 randomized, prospective study at 10 US centers, which compared the safety and effectiveness of PERLANE[®] and RESTYLANE[®] following treatment to baseline condition in 150 patients with pigmented skin and predominantly African American ethnicity. Patients were randomized to PERLANE[®] or RESTYLANE[®] 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.</p> <p>Effectiveness was studied with 6 month follow-up. Safety was studied with 6 months follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of PERLANE[®] at week 12 versus baseline condition on the visual severity of the NLFs.</p> <p>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 Perlane to Restylane.</p>

	<p>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 defined as 6 months or timepoint, if earlier, at which less than 50% of patients had at least a 1-grade response at both nasolabial folds.</p> <p>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.</p>																														
Outcomes	<p>Demographics:</p> <p>The study enrolled 150 patients with moderate to severe NLF wrinkles. The patients were predominantly healthy African-American females.</p> <p>Gender – Female: 140/150 (93%) Male 10/150 (7%)</p> <p>Ethnicity – White: 2 (1.3%); Hispanic or Latino: 9 (6%); African-American: 137 (91%); American Indian: 2 (1.3%)</p> <p>Fitzpatrick Skin Type – I to III: 0 (0%); IV: 44 (29%); V: 68 (45%); VI: 38 (25%)</p> <p>Efficacy:</p> <p>The results of the live blinded evaluator assessment of wrinkle severity for Perlane and control (Restylane) are presented in Table 8 and are based on the Intent-to-Treat analysis. In the primary effectiveness assessment at 12 weeks, 92% of the Perlane-treated and 93% of the Restylane-treated NLF maintained at least a 1 point improvement over baseline.</p> <table border="1" data-bbox="492 1477 1471 1720"> <thead> <tr> <th colspan="6">Table 8: Live Evaluator Wrinkle Severity Response Scores</th> </tr> <tr> <th>Time point</th> <th>No. of patients</th> <th>No. of PERLANE Pts. maintaining ≥ 1 Unit Improvement on WSRS</th> <th>95% PERLANE Confidence Interval</th> <th>No. of RESTYLANE Pts. maintaining ≥ 1 Unit Improvement on WSRS</th> <th>95% RESTYLANE Confidence Interval</th> </tr> </thead> <tbody> <tr> <td>6 weeks</td> <td>148</td> <td>140 (95%)</td> <td>90-99 %</td> <td>142 (96%)</td> <td>92-99%</td> </tr> <tr> <td>12 weeks</td> <td>149</td> <td>137 (92%)</td> <td>87-97%</td> <td>139 (93%)</td> <td>89-98%</td> </tr> <tr> <td>24 weeks</td> <td>147</td> <td>104 (71%)</td> <td>63-77%</td> <td>108 (73%)</td> <td>66-81%</td> </tr> </tbody> </table> <p>All p values <0.0001 based on t-test compared to baseline condition</p> <p>Antibody Testing:</p> <p>6/150 (4%) subjects displayed a pre-treatment antibody response against PERLANE® (which was believed to be related to co-purifying <i>Streptococcus</i> capsule antigens). No subjects developed a measurable increase in antibody titer after PERLANE® injection. 0/6 (0%) patients with antibodies against</p>	Table 8: Live Evaluator Wrinkle Severity Response Scores						Time point	No. of patients	No. of PERLANE Pts. maintaining ≥ 1 Unit Improvement on WSRS	95% PERLANE Confidence Interval	No. of RESTYLANE Pts. maintaining ≥ 1 Unit Improvement on WSRS	95% RESTYLANE Confidence Interval	6 weeks	148	140 (95%)	90-99 %	142 (96%)	92-99%	12 weeks	149	137 (92%)	87-97%	139 (93%)	89-98%	24 weeks	147	104 (71%)	63-77%	108 (73%)	66-81%
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	<p>PERLANE® had adverse experiences at the injection site as compared to the local adverse event rate observed in the entire PERLANE® population (<i>i.e.</i>, 14/150 (9%)). All the adverse experiences in the patients with a humoral response against PERLANE® were mild in severity. Immediate type skin testing demonstrated that no patient developed IgE to PERLANE®. Post-exposure histopathology of skin biopsies of an implant site on each patient demonstrated that no patient developed cell-mediated immunity to PERLANE®.</p>
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Non-U.S. Clinical studies

31GE0101: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	<p>1:1 randomized, prospective study at 6 Canadian centers, which compared the safety and effectiveness of PERLANE® and Hylaform®. Patients were randomized to either PERLANE® or Hylaform® in a “within-patient” model of augmentation correction of bilateral nasolabial folds (NLFs) 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 were partially masked; evaluating physicians were independent and masked; treating physicians were partially masked.</p> <p>Effectiveness was studied with 6 month follow-up. Safety was studied with 6 months follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: The difference in effect of PERLANE® as compared to Hylaform® on the visual severity of the NLFs, as assessed by a Blinded Evaluator at 6 months after baseline.</p> <p>The primary evaluation parameter was a five-step validated Wrinkle Severity Rating Scale (WSRS) score (absent, mild, moderate, severe, extreme) by the blinded evaluator at 6 months. Success was defined as maintaining at least a one point improvement of the NLF on the WSRS at 6 months after optimal correction was achieved. The percent of successful NLFs after Perlane and control treatments were compared, as well as a within-patient matched analysis (McNemar’s Test).</p> <p>Secondary: Wrinkle severity rating scale (WSRS) was assessed at other follow-up points (2 weeks and 3, 4.5 and 6 months after optimal correction) by the blinded evaluator and the patient. Global Aesthetic Improvement (GAI): very much improved /much improved / improved / no change / worse, assessed at same timepoints by patient.</p>

	Safety assessments included: investigator evaluation of adverse experiences at all time points.																																								
Outcomes	<p>Demographics:</p> <p>The study enrolled 150 patients with moderate to severe nasolabial fold wrinkles. The patients were predominantly healthy white females. The study was completed by 140 of 150 patients at six months and additional safety data were available in 122 of 150 patients at 9 months.</p> <p>Gender – Female: 140 (93%) Male: 10 (7%)</p> <p>Ethnicity – White: 142/150 (95%); Non-Caucasian: 8/150 (5%)</p> <p>Efficacy:</p> <p>The results of the blinded evaluator assessments are presented in Table 9 and are based on an Intent-to-Treat (ITT) analysis. At 6 months, 113/150 (75%) of the Perlane-treated NLFs maintained at least a single point improvement on the WSRS compared to 57/150 (38%) of the control-treated NLFs.</p> <table border="1"> <thead> <tr> <th colspan="4">Table 9: Blinded Evaluator Wrinkle Severity Response Rates</th> </tr> <tr> <th>Time point</th> <th>Number of NLFs</th> <th>No. of PERLANE NLFs maintaining ≥ 1 Unit Improvement on WSRS</th> <th>No. of Hylaform NLFs maintaining ≥ 1 Unit Improvement on WSRS</th> </tr> </thead> <tbody> <tr> <td>3 months</td> <td>150</td> <td>131 (87%)</td> <td>94 (63%)</td> </tr> <tr> <td>4.5 months</td> <td>150</td> <td>110 (73%)</td> <td>69 (46%)</td> </tr> <tr> <td>6 months</td> <td>150</td> <td>113 (75%)</td> <td>57 (38%)</td> </tr> </tbody> </table> <p>Table 10 shows the results for the within-patient investigator assessment of NLF on the WSRS.</p> <p>Table 10. Evaluating Investigator’s Assessment of NLF Severity; Score change from pre-treatment until 3, 4.5 and 6 months after last treatment</p> <table border="1"> <thead> <tr> <th>Mos. after last treatment</th> <th>Perlane is superior to Hylaform n (%)</th> <th>Perlane equal to Hylaform n (%)</th> <th>Hylaform superior to Perlane n (%)</th> <th>p-value*</th> </tr> </thead> <tbody> <tr> <td>3</td> <td>95 (63.3%)</td> <td>46 (30.7%)</td> <td>9 (6.0%)</td> <td>p< 0.001</td> </tr> <tr> <td>4 1/2</td> <td>87 (58.0%)</td> <td>54 (36.0%)</td> <td>9 (6.0%)</td> <td>p< 0.001</td> </tr> <tr> <td>6</td> <td>96 (64.0%)</td> <td>42 (28.0%)</td> <td>12 (8.0%)</td> <td>p< 0.001</td> </tr> </tbody> </table> <p>* McNemar’s test with % = n/N, where N = number of subjects in the ITT population</p>	Table 9: Blinded Evaluator Wrinkle Severity Response Rates				Time point	Number of NLFs	No. of PERLANE NLFs maintaining ≥ 1 Unit Improvement on WSRS	No. of Hylaform NLFs maintaining ≥ 1 Unit Improvement on WSRS	3 months	150	131 (87%)	94 (63%)	4.5 months	150	110 (73%)	69 (46%)	6 months	150	113 (75%)	57 (38%)	Mos. after last treatment	Perlane is superior to Hylaform n (%)	Perlane equal to Hylaform n (%)	Hylaform superior to Perlane n (%)	p-value*	3	95 (63.3%)	46 (30.7%)	9 (6.0%)	p< 0.001	4 1/2	87 (58.0%)	54 (36.0%)	9 (6.0%)	p< 0.001	6	96 (64.0%)	42 (28.0%)	12 (8.0%)	p< 0.001
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31GE0002: Prospective, Randomized, Blinded, Controlled Clinical Study

Design	1:1 randomized, prospective study at 2 Scandinavian centers, which compared the safety and effectiveness of PERLANE® and Zyplast®. Patients were randomized to either PERLANE® or Zyplast® in a “within-patient” model of augmentation
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	<p>correction of bilateral nasolabial folds (NLFs) with one treatment assigned to one side and the other treatment to the other side. Patients were partially masked; evaluating physicians were independent and masked; treating physicians were partially masked. A touch-up was allowed 2 weeks after initial treatment. Retreatment was allowed at 6 or 9 months.</p> <p>Effectiveness was studied with 9 months follow-up. Safety was studied with 12 months follow-up.</p>
Endpoints	<p>Effectiveness</p> <p>Primary: Superiority of correction of the NLF by PERLANE® as compared to Zyplast® based on the visual severity of the NLF as assessed by a Blinded Evaluator at 6 months after optimal correction was achieved.</p> <p>The primary evaluation parameter was a five-step validated Wrinkle Severity Rating Scale (WSRS) score (absent, mild, moderate, severe, extreme) by the blinded evaluator at 6 months. NLF success was defined as maintaining at least a one point improvement on the WSRS at 6 months after optimal correction was achieved. The within patent comparison of Perlane and control treatments was evaluated in a matched analysis (McNemar's Test).</p> <p>Secondary: Superiority of correction of the NLF by PERLANE® or Zyplast® based on the visual severity of the NLFs, as assessed by a Blinded Evaluator at 9 months after baseline.</p> <p>Safety assessments included: investigator evaluation of adverse experiences at all time points.</p>

Outcomes	Demographics:																									
	<p>The study enrolled 68 patients with correctable NLF wrinkles. The patients were predominantly healthy white females.</p> <p>Gender – Female: 65 (96%) Male: 3 (4%)</p> <p>Ethnicity – White: 68/68 (100%)</p> <p>Efficacy:</p> <p>The results of the blinded evaluator assessments are presented in Table 11. At the primary effectiveness time point of 6 months, the Perlane-treated NLF experienced more improvement from baseline (judged by the WSRS) in 50% of the subjects; the control-treated side experienced more improvement in 10.3% of the subjects.</p>																									
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How Supplied

PERLANE[®] is supplied in a 1 mL disposable glass syringe with a Luer-lok fitting. The gel particle contents of the syringe are sterile. A γ-irradiated sterilized needle, 27 G x ½”, is co-packed with each syringe. PERLANE[®] can be stored at a temperature of up to 25°C (77°F). Do not freeze and protect from sunlight. Refrigeration is not required.

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.

INSTRUCTIONS FOR USE CAN BE FOUND AT: <http://www.RestylaneUSA.com>

STORAGE

- PERLANE[®] should be stored at a temperature of up to 25°C (77°F). Do not freeze and protect from sunlight. Refrigeration is not required.

- PERLANE® is a gel without visible particulates. In the event that the contents of the syringe show signs of separation, do not use the syringe and notify Medicis Aesthetics Inc. at 1-866-222-1480.

US PATENT 5,827,937

Manufactured for

Medicis Aesthetics, Inc.
8125 N. Hayden Road
Scottsdale, AZ 85258
U.S.A.
Phone: 1-866-222-1480

Manufactured by

Q-Med AB
Seminariegratan 21
SE-752 28 Uppsala
Sweden

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[Cover]

Perlane®

Frequently Asked

Questions

[Inside Cover]

Perlane®

[Page 3]

Efficacy

Q What is *Perlane*® used for?

A *Perlane*® is used to smooth moderate to severe facial folds and wrinkles such as the lines from the nose to the corners of the mouth (nasolabial folds). *Perlane*® generally lasts for about 6 months. It has been found to be a safe dermal filler that restores volume and fullness to the skin.

Q How does *Perlane*® work?

A *Perlane*® is injected into the skin with an ultra-fine needle. It plumps the skin to smooth away wrinkles and folds. *Perlane*®'s water-loving nature attracts and binds water molecules to help maintain volume.

Perlane® is composed of hyaluronic acid, a natural substance that already exists in the body. The hyaluronic acid in *Perlane*® is a crystal clear gel that is chemically cross-linked (the long chemical strands are tied together) to delay breakdown by skin enzymes.

Perlane® is non-animal-based and free from animal protein. This quality prevents disease transmission. Allergy pre-testing is not necessary.

[Pages 4-6]

{Before and after photos}

[Page 7]

Q How long does *Perlane*[®] last?

A *Perlane*[®] is proven to deliver long-lasting results. Studies have shown that *Perlane*[®] effects generally last about six months as shown in the following graphs. *Perlane*[®] gradually disappears from the body without a trace.

[Page 8]

{Duration of efficacy graphs}

[Page 9]

Summary of results

Perlane[®] was studied in multiple clinical studies. In one, treatment of the nasolabial folds with *Perlane*[®] resulted in an improvement in wrinkles in 137 of 149 patients after three months, and 105 of 148 patients after six months. In another study, treatment of nasolabial folds with *Perlane*[®] resulted in an improvement in wrinkles in 122 of 141 patients after three months, and 88 of 138 patients after six months. Side effects were mild. Most of the side effects went away in seven days. *Perlane*[®] did not cause allergic reactions. See the patient diary information on page 12.

[Page 10]

Safety

Perlane[®] has been used safely by dermatologists and plastic surgeons since 2000 worldwide.

Q Who should not use *Perlane*[®] (Contraindications)?

A *Perlane*[®] should not be used by people with previous bad allergies (particularly to certain microorganisms known as gram positive bacteria), to drugs that have required in-hospital treatment, or in people with bleeding disorders. *Perlane*[®] should not be injected anywhere except the skin.

Q What are some warnings to consider?

A The use of *Perlane*[®] at sites with skin sores, pimples, rashes, hives, cysts, or infections should be postponed until healing is complete. Use of *Perlane*[®] in these instances could delay healing or make your skin problems worse.

You may experience skin discoloration (bruising), swelling, redness, tenderness, pain, itching, or small lumps in the area where you are injected. If any of these events occur, the majority usually last less than seven days. If any symptom lasts longer than two weeks, call the doctor who administered the *Perlane*[®] injection.

Inflammatory papules (red or swollen small bumps) may rarely occur. You may need antibiotics to treat them.

[Page 11]

Q What are some risks that may be experienced?

A As with all procedures like this, the injection of *Perlane*[®] carries a theoretical risk of infection and formation of scar tissue.

The safety and effectiveness of *Perlane*[®] have not been established in the treatment of lips, in nursing mothers, and in patients under 18 or over 65 years of age. Use of *Perlane*[®] in these ways could harm you or the nursing child.

The use of *Perlane*[®] in African-American patients can result in hyperpigmentation (darkening of skin color), which may take several weeks to correct.

If you have had herpes before, an injection can cause the herpes to come back.

The safety of *Perlane*[®] used with other skin therapies such as laser, mechanical or chemical peeling, and hair removal has not been established. The use of *Perlane*[®] in these skin therapies may not work or they may damage your skin.

You should avoid exposing the area(s) treated with *Perlane*[®] to excessive sun or UV

lamps, and extreme heat and cold until any redness or swelling has disappeared.

[Page 12]

Clinical Volunteers keeping diaries reported the following short-lived events:

These six graphs show what happened to patients each day after an injection of *Perlane*[®] as shown in diaries that they kept. They explain how many patients each day experienced pain (brown line), swelling (dark green line), redness (red line), tenderness (light blue line), bruising (dark blue line), and itching (green line). The lines go down with time because fewer and fewer patients reported these effects. The thickness of the line gives an indication of how bad the effect was—the thicker the line, the more patients thought the effect was not easily tolerable. The lines generally become thinner as time goes on, meaning that the effect becomes easier to live with over time.

All these events are worsened by rapid injection and other injection techniques that cause greater disruption of the skin. Injecting large amounts of *Perlane*[®] also increases these events.

{Tolerability Chart Legend}

Where lines on the graph are thicker the symptoms are less tolerable.

Thinner lines represent greater tolerability.

[Page 13]

{Tolerability Charts}

[Page 14]

Q What are the major side effects?

A Rarely, the doctor may inadvertently inject the product into a blood vessel, which can cause injury to the blood supply and damage to the skin.

Rarely, a few people have developed infections of the gel that must be treated with antibiotics or other treatment. Infection of the gel may be hard to treat, but will always go away when the gel is absorbed.

Q What should patients do prior to treatment?

A *Perlane*[®] requires no pretesting, but you should take a few precautions before being treated. Avoid using St. John's Wort, high doses of Vitamin E supplements, aspirin, and other non-steroidal anti-inflammatory medications, such as ibuprofen prior to treatment, because these may increase bruising or bleeding at the injection site. Also, if you have previously suffered from facial cold sores, discuss this with your physician. He or she may consider prescribing a medication to minimize recurrence.

[Page 15]

Q Do the injections hurt?

A *Perlane*[®] is injected directly into the skin in tiny amounts by an ultrafine needle. To help maximize your comfort, you should discuss the use of numbing medicines with your doctor before treatment.

Q How much do *Perlane*[®] treatments cost?

A *Perlane*[®] is a customized procedure based on your specific needs, so the cost will vary from patient to patient. In general, the cost of *Perlane*[®] is comparable to the cost of similar procedures. Because *Perlane*[®] is long lasting, it may prove to be very economical over the long term. Please ask your doctor to give you an estimate of the cost.

[Page 16]

Troubleshooting

Q What should I call my doctor about after the treatment?

A Most side effects like bruising, swelling, pain, tenderness, redness, and itching will usually go away within a week. Call your doctor if you have persistent problems beyond 14 days.

Blisters or skin sores may signal that you are having a recurrent herpes infection that should be treated.

You can develop an infection that should be treated with antibiotics. If you experience redness, tenderness and pain that does not go away you should call your doctor.

[Page 17]

Administration

Q What is the dose of *Perlane*[®]?

A The amount used depends on your face and what you would like to have treated. The average patient who has all of the severe wrinkles around the mouth corrected will use less than half of a tablespoon.

[Page 18]

Post-Treatment Checklist

Please observe the following after treatment with *Perlane*[®]:

- Cold compresses (a cloth dipped in cold water, wrung out, and applied to the injected area) may be used immediately after treatment to reduce swelling.
- Avoid touching the treated area within six hours following treatment so you do not accidentally injure your skin while the area is numb. After that, the area can be gently washed with soap and water.
- Until there is no redness or swelling, avoid exposure of the treated area to intense heat (sun lamp or sun bathing).
- If you have previously suffered from facial cold sores, there is a risk that the needle punctures could contribute to another occurrence. Speak to your physician about medications that may minimize a recurrence.
- Avoid taking aspirin, non-steroidal anti-inflammatory medications, St. John's Wort, and high doses of-vitamin E supplements for one week after treatment. These agents may increase bruising and bleeding at the injection site.

[back cover]

Perlane[®]

User Assistance Information

Your questions about *Perlane*[®] can be personally answered by contacting the Medicis toll-free call center, 24-hours per day, 7-days per week:

1-800-900-6389.

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