DIRECTIONS FOR USE - USA

Restylane® Defyne

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1 DEVICE DESCRIPTION

Restylane® Defyne is a sterile, biodegradable, viscoelastic, non-pyrogenic, clear, colorless and homogeneous soft hyaluronic acid gel. *Restylane® Defyne* is crosslinked with BDDE (1.4-butanediol diglycidylether). The product has a sodium hyaluronate concentration of 20 mg/mL in phosphate buffered saline at pH 7 and contains 3 mg/mL lidocaine hydrochloride.

2 INTENDED USE/INDICATIONS

Restylane® Defyne is indicated for injection into the mid-to-deep dermis for correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds) in patients over the age of 21.

Restylane® Defyne is indicated for injection into the mid-to deep dermis (subcutaneous and/or supraperiosteal) for augmentation of the chin region to improve the chin profile in patients with mild to moderate chin retrusion over the age of 21.

3 CONTRAINDICATIONS

- *Restylane® Defyne* is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- *Restylane® Defyne* may contain trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- *Restylane® Defyne* contains lidocaine and is contraindicated for patients with a history of allergies to such material or other amide type local anesthetics.

4 WARNINGS

- Defer use of *Restylane® Defyne* at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the underlying process has been controlled.
- *Restylane® Defyne* must not be implanted into blood vessels and should not be used in vascular rich areas. Localized superficial necrosis and scarring may occur after injection in or

near vessels. It is thought to result from the injury, obstruction, or compromise of blood vessels. Special caution should be taken if the patient has undergone a prior surgical procedure in the planned treatment area.

- Introduction of *Restylane® Defyne* into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur (see Health Care Professional Instructions).
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules should be considered and treated as a soft tissue infection. For additional information please see Adverse Events section.

For additional information, please see the Post-Marketing Surveillance in Adverse Events.

5 PRECAUTIONS

- *Restylane® Defyne* is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- In order to minimize the risks of potential complications, this product should only be used by health care practitioners who have appropriate training, experience and knowledge about the anatomy at and around the site of injection in order to minimize the risks of potential complications (perforation or compression of vessels, nerves and other vulnerable structures).
- The safety and effectiveness other than for the treatment of chin and nasolabial folds have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- *Restylane® Defyne* is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- *Restylane® Defyne* should not be mixed with other products before implantation of the device.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- Injection of *Restylane® Defyne* in patients with pre-existing tendency toward edema formation may be associated with prominent discoloration and excessive swelling due to fluid build-up.
- Injection of *Restylane® Defyne* too superficially or in facial areas with limited soft tissue support, thin skin or limited soft tissue cover, may result in contour irregularities and palpable lumps.

- *Restylane® Defyne* should be used with caution in patients on immunosuppressive therapy.
- This product should be used with caution in patients with a tendency to form hypertrophic scars or any other healing disorders.
- *Restylane® Defyne* should be used with caution in patients with bleeding disorders.
- Avoid injecting the product into areas in close proximity to a permanent implant, as this could potentially aggravate latent adverse events or interfere with the aesthetic outcome of the treatment. Limited data is available on injecting *Restylane® Defyne* into an area where an implant other than hyaluronic acid has been placed.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures at least until any initial swelling and redness has resolved.
- If epilation, UV radiation or laser treatment, mechanical or chemical peeling or any other procedure based on active dermal response is considered after treatment with *Restylane® Defyne*, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if *Restylane® Defyne* is administered before the skin has healed completely after such a procedure.
- Injections of *Restylane® Defyne* into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Post inflammatory pigmentation changes may occur after dermal filler injections in people with dark skin (Fitzpatrick Type IV-VI). Keloid formation was not observed in studies involving 421 patients whereof 49 patients with Fitzpatrick Type V-VI.
- After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- Individual variation and treatment area may affect the bio-degradation of *Restylane® Defyne,* and product might be detected in the tissue even after the clinical effect has disappeared.
- *Restylane® Defyne* injectable gel 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; notify Galderma Laboratories, L.P. at 1-855-425-8722.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer lock and needle hub connection.
- Based on clinical studies, the maximum recommended injected volume per patient and treatment for the treatment of moderate to severe nasolabial folds is 4 mL. For augmentation of the chin region to improve the chin profile, the maximum recommended injected volume per patient and treatment is also 4 mL (i.e., 2 mL in the chin and 2 mL in the area inferior to the lower lip, between the two lines from oral commissures up to the pre-jowl sulcus). The safety of injecting greater amounts has not been established.
- Considerations should be given to the total dose of lidocaine administered if dental block or topical administration of lidocaine is used concurrently. High doses of lidocaine (more than 400 mg) can cause acute toxic reactions manifesting as symptoms affecting the central nervous system and cardiac conduction.
- Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type anesthetics, e.g. certain anti-arrhythmics, since the systemic toxic effects can be additive.
- Lidocaine should be used cautiously in patients with epilepsy, impaired cardiac conduction,

severely impaired hepatic function or severe renal dysfunction.

6 ADVERSE EVENTS

A. Clinical Evaluation of Restylane® Defyne

Pivotal Study for *Restylane® Defyne* in correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds)

One hundred sixty two (162) subjects were enrolled in a randomized, double-blinded (subject and evaluator), active controlled, split-face comparison clinical trial to evaluate the safety and effectiveness of *Restylane® Defyne* vs. a non-lidocaine-containing comparator. Touch-up treatments occurred approximately 3 weeks after initial injection, as needed to achieve volume correction. After 48 weeks, subjects could opt for retreatment with *Restylane® Defyne* to both sides of the face, with a subsequent touch-up as needed 3 weeks afterwards. One hundred twenty four subjects (124, 76.5%) opted for retreatment.

Pre-printed diary forms were used by subjects for subject-reported assessments of specific signs and symptoms experienced during each of the first 21 days after initial, touch-up, and repeat treatments. Subjects rated each treatment site response as “Mild”, “Moderate”, “Severe” or “None.” Of the 162 subjects who received treatment, 98.8% (160 subjects) completed the diary forms. Of the 124 subjects who opted for retreatment, 100% of subjects completed the diary forms after retreatment.

After initial treatment, subjects rated pre-defined treatment site responses (redness, swelling, bruising, lump/bump formation, pain/tenderness, and itching) as predominantly mild or moderate in severity (Table 1), typically with a duration of 1 to 2 weeks (Table 2). Based on data from 124 subjects, no increase in frequency or in severity of signs/symptoms was observed following the retreatment injection or retreatment touch-up injection.

The trend in adverse events remained the same across subject skin types. Among the 73 subjects of Fitzpatrick Skin Types IV, V, and VI (27 of which were of Skin Type V or VI) in the study, no cases of keloid formation or of hyperpigmentation were reported.

Treatment site responses reported in subject diaries that lasted longer than 3 weeks were considered adverse events (AEs). AEs were also reported by the Treating Investigator at all follow-up visits where applicable.

Among the 162 treated subjects, 11.7% (19/162) experienced device- and injection-related AEs following initial and touch-up treatment, as well as retreatment and touch-up treatment. These subjects reported a total of 19 events related to control treatment and 20 events related to *Restylane® Defyne*. The most common of treatment site responses was injection site swelling, which was reported for 5 subjects. Injection site erythema and injection site pain were reported for 4 and 2 subjects, respectively. Other treatment site responses (inflammation, hematoma, discomfort, and mass) were reported for 1 subject each. Other related adverse events included skin tightness, dermatitis allergic, interstitial granulomatous dermatitis, salivary hypersecretion, sensitivity of teeth, presyncope, and arterial stenosis which were all reported for 1 subject each.

Seven subjects reported 8 serious adverse events (SAEs) that were considered to be unrelated to the device. The events were metastatic lung cancer, colon cancer, small bowel obstruction with uterine fibroid tumors, benign cyst on the right ovary, herpes zoster (shingles), febrile diarrhea, and lumbar spinal stenosis resulting in a spinal fusion.

Treatment site responses after initial treatments are summarized by severity in Table 1 and by duration in Table 2.

Table 1 - Treatment Site Responses by Maximum Severity Occurring In Subjects After Initial Treatment

	Restylane® Defyne (N=162) n (%)				**Control (N=162) n (%)**			
	Mild	**Moderate**	**Severe**	**Total**	**Mild**	**Moderate**	**Severe**	**Total**
Post-Initial Injection[a] (N= 160 for Restylane® Defyne and N= 160 for the control)								
Redness	66 (41.3)	27 (16.9)	8 (5.0)	101 (63.1)	65 (40.6)	27 (16.9)	9 (5.6)	101 (63.1)
Swelling	60 (37.5)	45 (28.1)	14 (8.8)	119 (74.4)	61 (**38**.1)	42 (26.3)	15 (9.4)	118 (73.8)
Bruising	48 (30.0)	36 (22.5)	11 (6.9)	95 (59.4)	47 (29.4)	37 (23.1)	13 (8.1)	97 (60.6)
Lump/Bump Formation	51 (31.9)	39 (24.4)	15 (9.4)	105 (65.6)	43 (26.9)	37 (23.1)	14 (8.8)	94 (58.8)
Pain/Tenderness	64 (40.0)	28 (17.5)	8 (5.0)	100 (62.5)	60 (37.5)	23 (14.4)	11 (6.9)	94 (58.8)
Itching	28 (17.5)	9 (5.6)	3 (1.9)	40 (25.0)	24 (15.0)	8 (5.0)	1 (0.6)	33 (20.6)

Percentages are based on total number of subjects who reported local tolerability assessments in a subject diary.

[a] Number of subjects who completed subject diaries.

Table 2 - Duration of Treatment Site Responses Occurring In Subjects After Initial Treatment

Injection site response	Restylane® Defyne (N=162) n (%)				Control (N=162) n (%)			
Duration[a]	**1-3 Days**	**4-7 Days**	**8-14 Days**	**>14 Days**	**1-3 Days**	**4-7 Days**	**8-14 Days**	**>14 Days**
Post-Initial Injection[b] (N= 160 for Restylane® Defyne and N= 160 for the control)								
Redness	74 (46.3)	19 (11.9)	6 (3.8)	2 (1.3)	72 (45.0)	22 (13.8)	6 (3.8)	1 (0.6)
Swelling	61 (38.1)	31 (19.4)	22 (13.8)	5 (3.1)	57 (35.6)	32 (20.0)	20 (12.5)	9 (5.6)
Brusing	25 (15.6)	42 (26.3)	23 (14.4)	5 (3.1)	29 (18.1)	32 (20.0)	35 (21.9)	1 (0.6)
Lump/bump Formation	34 (21.3)	35 (21.9)	12 (7.5)	24 (15.0)	40 (25.0)	15 (9.4)	15 (9.4)	24 (15.0)
Pain/tenderness	63 (39.4)	26 (16.3)	7 (4.4)	4 (2.5)	58 (36.3)	22 (13.8)	11 (6.9)	3 (1.9)
Itching	29 (18.1)	8 (5.0)	2 (1.3)	1 (0.6)	24 (15.0)	7 (4.4)	2 (1.3)	0

Percentages are based on total number of subjects who reported local tolerability assessments in a subject diary.
[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.
[b] Number of subjects who completed subject diaries.

Pivotal Study for *Restylane® Defyne* for augmentation of the chin region to improve the chin profile

One hundred forty (140) subjects were enrolled in a randomized, no-treatment-controlled, evaluator-blinded, multicenter study to evaluate the effectiveness and safety of *Restylane® Defyne* for the augmentation of the chin region to improve the chin profile. A touch-up treatment was offered after 4 weeks if optimal correction was not achieved at the initial treatment. Out of the 107 subjects randomized to treatment, 78 had the touch-up done at Week 4. At week 48, subjects in the no-treatment control group were offered an optional treatment and subjects in the treatment group were offered an optional additional treatment, 58 subjects in the treatment group and 23 subjects in the no-treatment control group opted for the offered treatment.

The key safety outcomes for this study are presented below in Tables 3 - 8. Subject reported injection related events are presented in Table 3 - Table 7. Adverse events (AEs) are presented in Table 8.

Pre-defined Injection Related Events:

Subjects evaluated injection related events (IREs) in a 28-day diary following initial treatment, and touch-up and retreatment, if performed. The presence of pre-defined expected post-treatment

events, i.e., pain, tenderness, redness, bruising, swelling, itching, lumps/bumps, and skin discoloration were assessed for the treated area(s). Subjects recorded the presence and level of severity (i.e., none, tolerable, affects daily activities, or disabling) for each of the pre-defined events.

Tenderness, pain, swelling, and lumps/bumps, respectively, were the most commonly reported IREs after initial treatment (112/125 [89.6%]; 92/125 [73.6%]; 92/125 [73.6%]; 88/125 [70.4%] subjects) with *Restylane® Defyne*. Similarly, tenderness, pain, and swelling were commonly reported post touch-up (62/78 [79.5%]; 49/78 [62.8%]; 49/78 [62.8%] subjects) and post-re-treatment (44/58 [75.9%]; 38/58 [65.5%]; 35/58 [60.3%] subjects).

For each treatment period, at least 80% (90/112) of subjects with tenderness, 78% (72/92) of subjects with pain, and 85% (78/92) of subjects with swelling reported it as tolerable.

A total of 6 subjects identified an IRE to be disabling after injection with *Restylane® Defyne*. Pain (including burning) was the most commonly reported disabling IRE (2 subjects [1.6%] post-initial injection and 1 [1.3%] post-touch-up injection); all other IREs (tenderness, lumps/bumps, and bruising) identified as disabling were reported by a single subject each.

For those subjects who experienced pain after treatment with *Restylane® Defyne* it generally lasted between 1-3 days (initial [55/92 subjects; 60%], touch-up [32/49 subjects; 65%], re-treatment [19/38 subjects; 50%]). Of the subjects who experienced tenderness it tended to last between 1–7 days after injections (initial [75/112 subjects; 67%], touch-up [52/62 subjects; 84%], and re-treatment [30/44 subjects; 68%]) with investigational treatment. Of the subjects who experienced swelling it also tended to last between 1–7 days after injections (initial [84/92 subjects; 91%], touch-up [42/49 subjects; 86%], and re-treatment [27/35 subjects; 77%]) with *Restylane® Defyne*.

Lumps/bumps was the IRE most frequently reported by subjects to last longer than 14 days after injections with *Restylane® Defyne* (initial [26/88 subjects; 30%], touch-up [8/38 subjects; 21%], and re-treatment [11/34 subjects; 32%]).

Subjects typically reported IREs at a lower incident rate, lower severity, and shorter duration following touch-up and re-treatment, when compared to initial treatment.

Table 3 - Pre-defined Injection Related Events by Maximum Severity Occurring in Subjects After Initial Treatment (Safety Population)

	Post Initial Injection with *Restylane® Defyne* (N=125) n (%)			
Diary Symptoms	**Total % (n/N)[a]**	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Any Symptom	92.8 (116/125)	71.6 (83/116)	25.9 (30/116)	2.6 (3/116)
Pain (including burning)	79.3 (92/116)	78.3 (72/92)	19.6 (18/92)	2.2 (2/92)
Tenderness	96.6 (112/116)	80.4 (90/112)	18.8 (21/112)	0.9 (1/112)
Redness	55.2 (64/116)	89.1 (57/64)	10.9 (7/64)	0
Bruising	73.2 (85/116)	80.0 (68/85)	20.0% (17/85)	0
Swelling	79.3 (92/116)	84.8 (78/92)	15.2 (14/92)	0
Lumps/bumps	75.9 (88/116)	90.9 (80/88)	9.1 (8/88)	0
Itching	33.6 (39/116)	92.3 (36/39)	7.7 (3/39)	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary.

[a] Number of subjects who completed at least one diary entry.

Table 4 - Pre-defined Injection Related Events by Maximum Severity Occurring in Subjects After Re-treatment (Safety Population)

Diary Symptoms	Post Re-treatment Injection with *Restylane*® *Defyne* (N=58) n (%)			
	Total % (n/N)[a]	**Tolerable %**	**Affects Daily Activities %**	**Disabling %**
Any Symptom	75.9 (44/58)	81.8 (36/44)	13.6 (6/44)	4.5 (2/44)
Pain (including burning)	86.4 (38/44)	86.8 (33/38)	13.2 (5/38)	0
Tenderness	100.0 (44/44)	90.9 (40/44)	9.1 (4/44)	0
Redness	54.5 (24/44)	95.8 (23/24)	4.2 (1/24)	0
Bruising	72.3 (32/44)	93.8 (30/32)	3.1 (1/32)	3.1 (1/32)
Swelling	79.5 (35/44)	88.6 (31/35)	11.4 (4/35)	0
Lumps/bumps	77.3 (34/44)	85.3 (29/34)	11.8 (4/34)	2.9 (1/34)
Itching	27.3 (12/44)	100.0 (12/12)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary.

[a] Number of subjects who completed at least one diary entry.

Table 5 - Duration of Pre-defined Injection Related Events Occurring in Subjects After Initial Treatment (Safety Population)

Diary Symptom	Post-Initial Injection[b] with *Restylane*® *Defyne* (N=125) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27 Days	28 Days[c]
Pain	55 (44.0)	27 (21.6)	8 (6.4)	1 (0.8)	1 (0.8)
Tenderness	35 (28.0)	40 (32.0)	31 (24.8)	4 (3.2)	2 (1.6)
Redness	47 (37.6)	8 (6.4)	7 (5.6)	2 (1.6)	0
Bruising	11 (8.8)	39 (31.2)	32 (25.6)	3 (2.4)	0
Swelling	52 (41.6)	32 (25.6)	4 (3.2)	3 (2.4)	1 (0.8)
Lumps/Bumps	20 (16.0)	20 (16.0)	22 (17.6)	17 (13.6)	9 (7.2)
Itching	27 (21.6)	5 (4.0)	3 (2.4)	4 (3.2)	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

Table 6 - Duration of Pre-defined Injection Related Events Occurring in Subjects After Touch-Up Treatment (Safety Population)

Diary Symptom	Post-Touch-Up Injection[b] with *Restylane® Defyne* (N=78) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27 Days	28 Days[c]
Pain	32 (41.0)	14 (17.9)	3 (3.8)	0	0
Tenderness	29 (37.2)	23 (29.5)	8 (10.3)	1 (1.3)	1 (1.3)
Redness	28 (35.9)	4 (5.1)	2 (2.6)	0	0
Bruising	8 (10.3)	21 (26.9)	11 (14.1)	0	0
Swelling	25 (32.1)	17 (21.8)	6 (7.7)	1 (1.3)	0
Lumps/Bumps	7 (9.0)	14 (17.9)	9 (11.5)	5 (6.4)	3 (3.8)
Itching	14 (17.9)	3 (3.8)	3 (3.8)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary.

Table 7 - Duration of Pre-defined Injection Related Events Occurring in Subjects After Re-treatment (Safety Population)

Diary Symptom	Post-Re-treatment Injection[b] with *Restylane® Defyne* (N=58) n (%)				
	Duration[a]				
	1–3 Days	4–7 Days	8–14 Days	15-27Days	28 Days[c]
Pain (including burning)	19 (32.8)	16 (27.6)	2 (3.4)	1 (1.7)	0
Tenderness	13 (22.4)	17 (29.3)	12 (20.7)	2 (3.4)	0
Redness	14 (24.1)	7 (12.1)	2 (3.4)	1 (1.7)	0
Bruising	7 (12.1)	12 (20.7)	12 (20.7)	1 (1.7)	0
Swelling	11 (19.0)	16 (27.6)	8 (13.8)	0	0
Lumps/Bumps	4 (6.9)	8 (13.8)	11 (19.0)	5 (8.6)	6 (10.3)
Itching	6 (10.3)	5 (8.6)	1 (1.7)	0	0

Note 1: Percentages are based on total number of subjects who reported local tolerability assessments in the subject diary. Duration = Number of days with symptoms

[a] Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

[b] Number of subjects who completed at least one diary entry.

[c] Subject diary was only collected for 28 days. Events with a duration of 28 days were ongoing at the end of the subject diary

Device and Injection Related Events: AEs were evaluated by Investigators throughout entirety of the study. An overall summary of AEs following initial and touch-up treatment is presented in Table 8.

The majority of subjects reported no AEs across all treatment periods (no treatment at baseline [27/33, 81.8%]; initial treatment [88/129, 68.2%]; re-treatment [54/58, 93.1%]). Overall, 51 subjects reported a total of 81 AEs across all treatment periods (no treatment at baseline [6/33, 18.2%]; initial treatment [41/129, 31.8%]; re-treatment [4/58, 6.9%]). All of the 81 AEs reported were classified as either mild (62/81 [76.5%]) or moderate (19/81 [23.5%]); no severe AEs were reported during the study. There was one SAE during the study experienced by 1 (0.8%) subject that was not related the investigational treatment or procedure (stage IV metastatic lung cancer).

A total of 25 AEs were related to the investigational treatment or injection procedure and were reported either after initial treatment (18/129 [14.0%]) or re-treatment (1/58 [1.7%]) with *Restylane® Defyne*.

In terms of onset time, the median onset for related AEs was at the day of treatment with *Restylane® Defyne* (mean, 11.5 days). One subject experienced delayed implant site swelling in

the chin of mild severity 185 days after initial treatment with *Restylane® Defyne* that lasted 4 days and resolved following treatment.

There were no ongoing AEs at the end of the study. After treatment with *Restylane® Defyne,* most related AEs resolved within approximately a week (8 days).

The severity and duration of treatment related AEs occurring in <5% of subjects in either treatment group are summarized in Table 9 - Chin function and sensation evaluations for all subjects at all visits were assessed as normal. For device palpability, at least 95.5% of subjects had normal (expected feel) of the chin following treatment with *Restylane® Defyne*.

Table 8 - Summary of Adverse Events After Initial/Re-treatment (Safety Population)

	Initial Treatment with *Restylane® Defyne* (N=129)		**Re-treatment with *Restylane® Defyne* (N=58)**	
	Subjects n (%)	**Events**	**Subjects n (%)**	**Events**
AEs Overall	47 (36.4)	77	4 (6.9)	4
Any AE Related to Study Product or Injection Procedure				
Total	18 (14.0)	24	1 (1.7)	1
Mild	17 (94.4)	23	1 (100)	1
Moderate	1 (5.6)	1	0	0
Severe	0	0	0	0
Action Required				
None	8 (44.4)	12	0	0
Medication	10 (55.6)	12	1(100)	1
Non-Pharmacological	1 (5.6)	1	0	0
Withdrawal	0	0	0	0
Mean Onset of Related AEs (days)	11.5	24	0.0	1
Minimum	0	--	0	--
Maximum	185	--	0	--
Mean Duration of Related AEs (days)	13.1	24	4.0	1
Minimum	2	--	4	--
Maximum	112	--	4	--
Unrelated AEs to Study Product or Injection Procedures	29 (22.5)	47	3 (5.2)	3
Serious AEs (not related to the study product or injection procedure)	1 (0.8)	1	0	0
No AEs	88 (68.2)	--	54 (93.1)	--

Table 9 - Treatment Related Adverse Events Occurring <5% of Subjects by Maximum Severity after Initial/Re-treatment (Safety Population)

	Initial Treatment with *Restylane Defyne* (N=129)				Re-treatment with *Restylane Defyne* (N=58)			
Adverse Event	**Subjects n (%)**	**Mild %**	**Moderate %**	**Severe %**	**Subjects n (%)**	**Mild %**	**Moderate %**	**Severe %**
Implant site pain	6 (4.7)	5 (83.3)	1 (16.7)	0	1	1 (1.7)	0	0
Implant site bruising	3 (2.3)	3 (100)	0	0	0	0	0	0
Implant site swelling	3 (2.3)	3 (100)	0	0	0	0	0	0
Implant site erythema	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site haemorrhage	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site nodule	2 (1.6)	2 (100)	0	0	0	0	0	0
Implant site mass	1 (0.8)	1 (100)	0	0	0	0	0	0
Implant site oedema	1 (0.8)	1 (100)	0	0	0	0	0	0
Injection site eczema	1 (0.8)	1 (100)	0	0	0	0	0	0
Oral Herpes	1 (0.8)	1 (100)	0	0	0	0	0	0

Table is sorted in descending order by overall incidence rate.

Chin and Lower Lip Safety Assessments: Chin and lower lip sensation, lip movement, function, mass formation, and product palpability were performed at screening/baseline and all physical visits thereafter. The parameters for lip movement, function, mass formation and product palpability were rated as normal or abnormal. Lip function was graded separately from Chin function.

In the study, chin function and sensation evaluations for all subjects at all visits were assessed as normal. For device palpability, at least 95.5% of subjects had normal (expected feel) of the chin following treatment with *Restylane® Defyne*.

Additional Safety Assessments: Changes in hair growth in the treated area for male subjects were evaluated at physical follow-ups after baseline treatment; any changes were to be reported as AEs. There were no changes in hair growth assessed in male subjects for this study.

Exploratory Subgroup Analyses: Exploratory safety analyses by subgroup (i.e., gender, study site, median injection volume of $\leqslant$ 2.7 mL and > 2.7 mL, and FST) were evaluated. Some of the subgroup analyses of treatment-related AEs occurring in subjects after initial and re-treatment with *Restylane® Defyne* are summarized in Table 10.

A total of 7 of 11 study sites had subjects who experienced related AEs. The variability between sites (0-54%) may be explained by the relatively small sample size at each site.

This study stratified subjects by FST group (I-III, IV, or V-VI). There were no marked differences in proportion of subjects who experienced at least one related AE based on FST group, 12% vs. 16.7% vs. 16.7% for FST I-–III vs. IV vs. V-–VI skin types, respectively, in the initial treatment with *Restylane® Defyne* group. One subject (1/14 [7.1%]) who received a re-treatment with *Restylane® Defyne,* with FST IV, experienced at least one related AE.

Table 10 - Incidence of Related AEs after Initial/Re-treatment by Subgroup

Category	Initial Treatment with *Restylane® Defyne* % (N=129)	Re-treatment with *Restylane® Defyne* (N=58)
Gender		
Female	14.8 (17/115)	2.0 (1/51)
Male	7.1 (1/14)	0
Age Group		
20-29 years	21.4 (3/14)	0 (0/5)
30-50 years	19.2 (10/52)	0 (0/19)
>50 years	7.9 (5/63)	2.9 (1/34)
Median Injection Volume		
≤ 2.7 mL	13.8 (9/65)	0
>2.7 mL	14.1(9/64)	2.8 (1/36)
FST		
FST I-III	12.0 (9/75)	0
FST IV	16.7 (6/30)	7.1 (1/14)
FST V-VI	16.7 (4/24)	0

B. Other Safety Data

Post-Market Surveillance

The adverse event reports received from post-marketing surveillance (from voluntary reporting and published literature) for the use of *Restylane® Defyne* with and without lidocaine in the U.S. and other countries most commonly included reports of transient swelling/edema and with immediate onset or delayed onset, up to several weeks after treatment.

The following events were also reported in decreasing order of frequency:

- mass formation/induration
- papules/nodules
- erythema
- pain/tenderness
- short duration of effect
- bruising/hematoma
- presumptive bacterial infections and abscess formation
- inflammation
- discoloration
- injection site reactions including burning sensation, irritation and warmth
- ischemia and necrosis due to unintentional intravascular injection or embolization

- hypersensitivity/angioedema
- granuloma/foreign body reaction
- pruritus
- neurological symptoms including hypoaesthesia, paraesthesia and facial paralysis
- eye disorders such as eye swelling, eye pain, eyelid oedema, eyelid ptosis, blurred vision, ocular discomfort and visual impairment
- rash
- device dislocation
- blisters/vesicles
- symptoms of reactivation of herpes infection
- deformity/assymetry
- discharge
- atrophy/scarring
- urticaria
- capillary disorder such as telangiectasia
- dermatitis
- acne
- extrusion of device
- non-dermatological events including chills, discomfort, dizziness, headache, malaise, nausea and pyrexia and
- other dermatological events including pain of skin

When required, treatments for these events included ice, massage, warm compress, nitroglycerine paste, corticosteroids, antibiotics, antihistamines, analgesics, antiviral agents, diuretic agents, aspiration/incision, drainage, surgery or enzymatic degradation (with hyaluronidase) of the product.

Reports of serious adverse events for *Restylane® Defyne* with and without lidocaine are rare. The most commonly reported serious adverse events were infection/abscess, mass/induration ischemia/necrosis and eye disorders. Other concurrent serious events included: swelling, pain/tenderness, erythema and discolouration.

Serious infection/abscess were mostly reported with a time to onset ranging from one day up to 4 months following the injection. Most of the patients were recovering at the time of last contact. The treatments may include: antibiotics, analgesics, corticosteroids and hyaluronidase.

Serious mass/induration including granuloma/foreign body reaction was mostly reported with a time to onset ranging from a month to 4 months or longer. The outcome was mainly recovered or recovering at the time of last contact. Granuloma is rarely confirmed with histopathological for diagnosis. The treatments may include: analgesics, antihistamine, antibiotics, corticosteroids, excisions, and biopsy.

Symptoms of inflammation at the implant site commencing either shortly after injection or after a delay of up to several weeks have been reported. In case of unexplained inflammatory reactions infections should be excluded and treated if necessary since

inadequately treated infections may progress into complications such as abscess formation. Treatment using only oral corticosteroids without concurrent antibiotic treatment is not recommended.

Vascular occlusion resulting in ischemia/necrosis and visual disturbances, including blindness, have been reported following facial aesthetic treatments with injectable soft tissue fillers, with a time to onset ranging from immediate to a few weeks following injection. Vascular compromise may occur due to an inadvertent intravascular injection or as a result of local vascular compression by the implant. This may manifest as ischemia or necrosis at the implant site or in the area supplied by the blood vessels affected; or rarely as ischemic events in other organs due to embolization. Isolated, rare ischemic events affecting the eye and brain have led to vision loss and cerebral infarction, respectively. Vision abnormalities including blindness have been reported following injection of dermal fillers including HA, with and without lidocaine, into the nose, glabella, periorbital areas, and/or cheek, with a time to onset ranging from immediate to a few days following injection. Treatments may include anticoagulants, epinephrine, aspirin, hyaluronidase, corticosteroid treatment, analgesics, local vasodilating agents such as PDE-5 inhibitor and nitropaste, antibiotics, drainage, surgery, and hyperbaric oxygen. Outcomes ranged from resolved to ongoing at the time of last contact. In many of the events requiring medical intervention, the patient was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use.

Adverse reactions should be reported to Galderma Laboratories, L.P. at 1-855-425-8722.

7 CLINICAL STUDIES

7.1 Pivotal Study for Restylane® Defyne in correction of moderate to severe, deep facial wrinkles and folds (such as nasolabial folds)

Pivotal Study Design

A multi-center, double-blinded (subject and evaluator), randomized, active-controlled clinical study with a split-face design was conducted to evaluate the safety and effectiveness of *Restylane® Defyne* versus a comparator, a non-lidocaine HA dermal filler in the treatment of moderate to severe nasolabial folds. Subjects were randomized to treatment with *Restylane® Defyne* on either the right or left side of the face in a 1:1 ratio. The non-lidocaine containing comparator was injected into the other side of the face. Up to 2 initial treatments approximately 3 weeks apart (initial treatment and up to 1 touch-up treatment) and 48 weeks later up to 2 retreatments approximately 3 weeks apart (1 optional retreatment and up to 1 touch-up treatment) were allowed.

Treated subjects returned for routine safety visits with the Treating Investigator at 3, 12, 24, 36, and 48 weeks after the initial injection(s). All subjects returned for effectiveness follow-up visits with the evaluating investigators at 3, 12, 24, 36, and 48 weeks after the initial injection(s). The evaluating investigator assessed subjects' nasolabial folds on the validated 5-point Wrinkle Severity Rating Scale (WSRS). The subjects self-assessed the wrinkle severity on a 5-point scale and also used an 11-point Numeric Pain Intensity Scale (NPIS).

Study Endpoints

The primary effectiveness variable was the change in WSRS from Baseline to 24 weeks after treatment as assessed by the Blinded Evaluating Investigator compared to the control.

Secondary effectiveness endpoints included the difference in WSRS change from baseline to each visit up to Week 48 after treatment and WSRS response rate, defined as the percentage of subjects with at least a 1-grade improvement in WSRS from Baseline up to Week 48 after treatment. In addition, pain assessment after each injection (compared between treatments), the difference in subject self-assessment of wrinkle severity (SSA) response rate at weeks 3, 12, 24, 36, and 48 after treatment and the change from baseline in SSA score at weeks 3, 12, 24, 36, and 48 after treatment was also included.

Subject Demographics

A total of 162 subjects were randomized, 26 subjects prematurely discontinued the study, primarily due to subject request (42%, 11/26) or due to loss to follow-up (35%, 9/26).

At baseline, all subjects had moderate (73%, 118/162 on *Restylane® Defyne* treated side; 72%, 117/162 on Control treated side) or severe (27%, 44/162 on *Restylane® Defyne* treated side; 28%, 45/162 on Control treated side) WSRS scores for their nasolabial folds. The majority of the subjects self-assessed their wrinkle severity as either moderate (approximately 60%) or severe (approximately 30%). Subject demographics and pre-treatment characteristics are presented in Table 11.

Table 11 - Demographics and Pre-treatment Characteristics (N= 162) – All Subjects

Characteristic		**(N = 162)** **% (n)**
Gender	Female	96.3% (156)
	Male	3.7% (6)
Age (years)	Median	53.0
	Range (min, max)	(34-75)
Race	Caucasian	80% (129)
	Black	12% (20)
	Hispanic	6% (10)
	Other	2% (3)
Fitzpatrick Skin Type	I	4% (6)
	II	17% (28)
	III	41% (67)
	IV	21% (34)
	V	12% (19)
	VI	5% (8)

Primary Effectiveness Results

The primary endpoint of the study was met. The mean change from baseline to month 6 on the Wrinkle Severity Rating Scale (WSRS) was 1.1 for subjects treated with *Restylane® Defyne* and 1.1 for subjects treated with the control. The effect of *Restylane® Defyne* was demonstrated to be non-inferior to the control, with both products showing a clinically meaningful improvement in wrinkle severity. For the primary effectiveness variable of change from Baseline in WSRS at Week 24 post-treatment, both study products caused a mean reduction of similar magnitude. The two products' point estimates differed by -0.09 units (confidence interval -0.18 to -0.01). In addition, similar numbers of subjects experienced a 1-grade, 2-grade, or 3-grade improvement with both study products.

Throughout the follow-up period, *Restylane® Defyne* continued to provide a clinically significant improvement in wrinkle severity ($\geq$ 1-point mean improvement on the WSRS), with a majority of folds treated with *Restylane® Defyne* demonstrating improvement through 1 year (Table 12).

At 6 months, improvements in nasolabial folds ($\geq$ 1-point mean improvement on the WSRS) treated with *Restylane® Defyne* were observed in 77.1% (125/162) of subjects. At 1 year, 69.7% (104/149) of folds treated with *Restylane® Defyne* maintained improvement.

On Subject Self Assessment at 6 months, 77.8% (126/162) of subjects reported improvement in fold severity for the folds treated with *Restylane® Defyne*. At 1 year, 64.4% (96/149) of subjects reported improvement in folds treated with *Restylane® Defyne*.

Table 12 - Effectiveness Results Through 1 Year

	Restylane® Defyne % (n/N ITT)
Week 12	87.7% (142/162)
Week 24	77.1% (125/162)
Week 36	84.4% (125/148)
Week 48	69.7% (104/149)

Restylane® Defyne presented a statistically (p= <0.001) more favorable pain profile than the non-lidocaine containing control. At the time of injection, subjects rated their pain as 3.2 on a scale of 0 (no pain) to 10 (worst possible pain) for the side of the face treated with *Restylane® Defyne.* In comparison, subjects rated their pain as 5.3 on the same scale for the side of the face treated with the control. At the time of the initial injection until the 60-minute time point, subjects recorded more pain with the comparator than with *Restylane® Defyne*.

Subject Self-Assessments

Subjects performed self-assessments of wrinkle severity. Most subjects (77.8% at Week 24 and 64.4% at Week 48) had at least a 1-grade improvement in SSA scores with *Restylane® Defyne*.

7.2 Pivotal Study of Restylane® Defyne for augmentation of the chin region to improve the chin profile

Pivotal Study Design

A randomized, no-treatment-controlled, evaluator-blinded, multicenter study was conducted to evaluate the effectiveness and safety of *Restylane® Defyne* for augmentation of the chin region to improve the chin profile. Subjects were randomized to one initial treatment with *Restylane® Defyne* or no-treatment in a 3:1 ratio. A touch-up treatment was offered after 4 weeks if optimal correction was not achieved at the initial treatment. At week 48, subjects in the no-treatment control group were offered an optional treatment and subjects in the treatment group were offered an optional additional treatment.

Treated subjects returned for follow-up visits at Weeks 2, 4, 12, 24, 36 and 48 after the initial injection. If a touch-up was performed, additional visits at Week 2 and 4 after the touch-up visit were scheduled. If the subjects were treated at Week 48, follow-up visits at Weeks 2, 4 and 12 after the injection was performed. Evaluation of chin retrusion was done by the Treating Investigator and Blinded Evaluator using the Galderma Chin Retrusion Scale (GCRS). The Treating Investigator and subject assessed improvement on the Global Aesthetic Improvement Scale (GAIS). Subjects self-assessed their satisfaction with treatment outcome using a FACE-Q Satisfaction with Chin questionnaire.

Study Endpoints

The primary objective of the study was to evaluate the effectiveness of *Restylane® Defyne* versus a no-treatment control in the augmentation of the chin region to improve the chin profile by comparing response rates, defined by at least 1-point improvement from baseline using the Galderma Chin Retrusion Scale (GCRS), as assessed by the Blinded Evaluator. The assessment was done at 12 weeks after last injection for the treatment group or after baseline if randomized to no treatment.

Secondary effectiveness endpoints included subjects' satisfaction change from baseline in the FACE-Q satisfaction with chin questionnaire at 12 weeks after last injection for the treatment group or after baseline for the no-treatment controls and at 24, 36 and 48 weeks and correction of chin retrusion using the GCRS as assessed by the Blinded Evaluator at 24, 36 and 48 weeks after last injection for the treatment group or after baseline for the no-treatment controls. In addition, evaluation of aesthetic improvement using GAIS at 12, 24, 36 and 48 weeks after the last injection for the treatment group or after baseline if randomized to no treatment, volume change over time by digital 3D photography at 12, 24, 36 and 48 weeks after the last injection or after baseline for the no-treatment controls was included. In addition, an Independent Photographic Reviewer's assessment of improvement in chin retrusion by comparison of random, blinded pairings of the baseline and post-baseline photographs from physical visits at 12, 24, 36 and 48 weeks.

Subject Demographics

A total of 140 subjects were randomized, 17 prematurely withdrew from the study due to subject request (3.6%, 5/140), lost to follow up (7.9%, 11/140) or move out of state (0.7%, 1/140). No subject discontinued the study for medical reasons.

At baseline, all subjects had mild (40%, 56/140) or moderate (60%, 84/140) chin retrusion scores on the GCRS as assessed by the Blinded Evaluator. Subject demographics are presented in Table 13.

Table 13 - Demographic Characteristics - all subjects

Parameter		**(N=140)**
Age (years)	Median	49.5
	Min, Max	20, 73
Gender	Female	125 (89.3%)
	Male	15 (10.7%)
Race	White	106 (75.7%)
	Black or African American	17 (12.1%)
	Asian	9 (6.4%)
	American Indian or Alaska Native	0
	Native Hawaiian or Other Pacific Islander	1 (0.7%)
	Other	7 (5.0%)
Fitzpatrick Skin Types	I	8 (5.7%)
	II	35 (25.0%)
	III	40 (28.6%)
	IV	32 (22.9%)
	V	14 (10.0%)
	VI	11 (7.9%)

Effectiveness Results

The primary endpoint of the study was met. The responder rate (defined as at least one point improvement on the GCRS at Week 12) was 81.3% in the treatment group vs 6.1% in the no-treatment control. The difference was statistically significant ($p<0.001$).

The difference in responder rates remained statistically significant compared with no treatment throughout the follow-up period, at Weeks 24, 36 and 48.

- Subjects who were treated with *Restylane® Defyne* reported greater satisfaction with the appearance of their chin based on FACE-Q scores at Week 12, compared with no treatment; sensitivity and subgroup analyses confirmed the robustness of the primary analysis. The durability of the treatment response extended to the later assessments with change from baseline scores consistently greater in the *Restylane® Defyne* group compared with no treatment (Week 24, Week 36, and Week 48).

- The proportion of subjects who reported aesthetic improvements (improved, much improved or very much improved) in the chin area across the Week 12, Week 24, Week 36 and Week 48 assessments using the GAIS was substantially higher in the *Restylane® Defyne* group (84.8–99.0%), compared with the no treatment group (0–3.7%); Treating Investigators scored 96.0–100% of subjects in the *Restylane®*

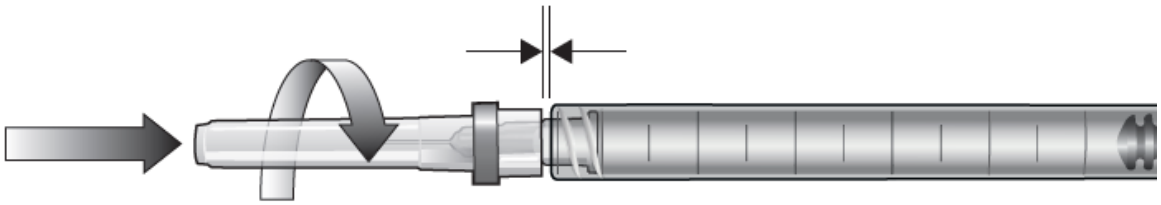
Defyne group as improved, compared with 0–3.3% of subjects in the no treatment group.

8 INSTRUCTIONS FOR USE

A. To Attach Needle to Syringe

Use surgical gloves, remove the cap from the needle and the tip cap from the syringe. Hold firmly around the syringe barrel and grasp the needle shield with the other hand. Screw the needle tight onto the syringe by simultaneously pushing and rotating firmly until the needle is completely locked. To ensure proper assembly, minimize the gap between the needle shield and the syringe. See the figure below.

Remove the needle shield just before injection by pulling it straight out. Do not rotate.
Note: Improper assembly may cause leakage or needle disconnection.



B. Health Care Professional Instructions

1. *Restylane® Defyne* is a cross-linked formulation resulting in a robust injectable gel that can be injected using a 27 G needle, for volumizing and contouring of facial wrinkles and folds.

2. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain maximum correction Pre-treatment photographs are recommended.

3. Although the study showed that lidocaine in *Restylane® Defyne* had an effect on pain, supplementary anesthesia may be used for additional pain management during and after injection.

4. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or other antiseptic.

5. To avoid breakage of the needle, do not attempt to bend or otherwise manipulate it before or during treatment. If needle gets bent, discard it and complete the procedure with a

replacement needle. Do not re-shield used needles. Recapping by hand is a hazardous practice and should be avoided. Discard unshielded needles in approved sharps collectors.

6. Before injection press the plunger rod carefully until a small droplet is visible at the tip of the needle.

7. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not in a blood vessel.

8. Inject *Restylane® Defyne* slowly by applying even pressure on the plunger rod with the thumb or palm of the hand. Do not apply excessive pressure to the syringe at any time. If resistance is encountered the needle should be partially withdrawn and repositioned or fully withdrawn and checked for function and replaced if needed.

9. After the first small amount of material has been injected into the patient, wait a few seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.

10. The injection technique and the depth of injection administered may vary based on the subject's treatment needs.
    a. Correction of moderate to severe, deep nasolabial folds
       A retrograde linear threading technique, serial puncture injections, or a combination of the 2 have been used to achieve optimal results. Injections should be done into the mid-to-deep dermis. Injecting the product too superficially may result in visible lumps and/or bluish discoloration.

    b. Augmentation of chin region to improve chin profile
       A linear antegrade and retrograde threading technique, serial puncture injections, fern pattern technique and fanning technique have been used to achieve optimal results. The product should be injected into the mid-to-deep dermis or in subcutaneous to supraperiosteal implantation.

11. It is important that the injection be 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. It is recommended to change needle for each new treatment site.

12. Injection volume to achieve optimal correction may vary based on the subject's treatment needs.
    a. Correction of moderate to severe, deep nasolabial folds
       The injection volume for the initial injection is generally about 1.4 mL per treatment site (NLF). Injection volume to achieve optimal correction (touch-up) and re-treatment is generally about 0.7 mL per treatment site.

       The maximum volume studied is 2 mL per NLF and treatment occasion.

    b. Augmentation of chin region to improve chin profile
       The initial injection volume is generally about 2.6 mL depending on severity of

chin retrusion. Injection volume to achieve optimal correction (touch-up) is generally about 1.4 mL. The injection volume for re-treatment is generally 2.1 mL.

Recommended maximum injected volume per patient for the initial and re-treatment injections is 4 mL for chin (2 mL in the chin and 2 mL in the area inferior to the lower lip, between the two lines from oral commissures up to the pre-jowl sulcus). For touch-up injections, the maximum volume studied is 2 mL.

13. Correct to 100% of the desired volume effect. Do not overcorrect.

14. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[1]

15. When injection is completed, the treated site may be gently massaged to mold the product to the contour of the surrounding tissue and assure that it is evenly distributed. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.

16. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient back to the office for a touch-up treatment.

17. Patients may experience treatment site responses, which typically resolve within 1 to 2 weeks. An ice pack may be applied for a short period following treatment to minimize swelling and reduce pain. Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.

18. The health care practitioner should instruct the patient to promptly report any problems associated with the use of *Restylane® Defyne*.

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[1] Alam, M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers *Dermatol Surg.* 2008;34(suppl 1):S115-S148.

C. Patient Instructions

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise and extensive sun or heat exposure. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the treatment sites.
- The patient should be asked to avoid touching or shaving the treated area and not to apply any creams or cosmetics in the treated area before the skin has healed completely in order to prevent infections or elicit an inflammatory reaction.
- If the treated area is swollen, an ice pack may be applied to the site for a short period.

9 HOW SUPPLIED

Restylane® Defyne injectable gel is supplied in individual treatment syringes with needles as indicated on the carton. The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile. Do not resterilize. Do not use if package is open or damaged.

10 SHELF LIFE AND STORAGE

Restylane® Defyne must be used prior to the expiration date on the package. Store at a temperature of up to 25ºC/77ºF. Do not freeze. Protect from sunlight. Refrigeration is not required.

Restylane® Defyne injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Galderma Laboratories, L.P. immediately at 1-855-425-8722

Do not use if the package is damaged or if expiry date or lot number is missing or illegible. Immediately return the damaged product to Galderma Laboratories, L.P.

To place an order, contact. Galderma Laboratories, L.P. at 1-855-425-8722

Rx only

U.S. Patent 8,357,795; 8,450,475; 8,822,676

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