

## **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 with a high lifting capacity. 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.

#### **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

#### **4. WARNINGS**

- 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.

- Product use at sites in which an active skin disease is present, such as inflammation, infection, or tumors, should be deferred until the underlying process has been controlled.

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.
- The safety and effectiveness for the treatment of anatomic regions other than the facial wrinkles and 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.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- Restylane Defyne should be used with caution in patients on immunosuppressive therapy.
- Restylane Defyne should be used with caution in patients with bleeding disorders.
- Do not inject the product in a site that has been treated with a permanent implant.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- If laser treatment, 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.
- 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.
- 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.
- 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 who are knowledgeable about the anatomy at and around the site of injection.
- 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.
- 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.

## **6. ADVERSE EVENTS**

### **A. Clinical Evaluation of Restylane Defyne**

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.

Preprinted 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 intensity (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 intensity 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
<b>Post-Initial Injection<sup>a</sup> (N= 160 for Restylane Defyne and N= 160 for the control)</b>								
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.

<sup>a</sup> 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 (%)			
	1-3 Days	4-7 Days	8-14 Days	>14 Days	1-3 Days	4-7 Days	8-14 Days	>14 Days
<b>Post-Initial Injection<sup>b</sup> (N= 160 for Restylane Defyne and N= 160 for the control)</b>								
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)
Bruising	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.

<sup>a</sup> Number of days was defined as the sum of days when a sign/symptom was scored 'Mild' or higher.

<sup>b</sup> Number of subjects who completed subject diaries.

## 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 embolisation
- hypersensitivity/angioedema
- granuloma/foreign body reaction
- pruritus

- neurological symptoms including hypoesthesia, 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, eye disorders. Other concurrent serious events included: swelling, pain/tenderness, erythema and discoloration.

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.

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. 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.

## **7. CLINICAL STUDIES**

### **A. Pivotal Study for Restylane Defyne**

#### **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, 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, 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.

## **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 3.

**Table 3 - 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 4).



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 4 - Effectiveness Results Through 1 Year**

	<b>Restylane Defyne % (n/N ITT)</b>
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.

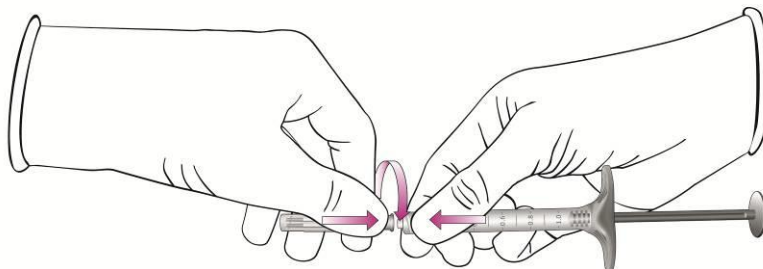
### **Subject Self-Assessments**

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.

## **8. INSTRUCTIONS FOR USE**

### **A. To Attach Needle to Syringe**

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



## **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.
6. Before injection press the plunger rod carefully until a small droplet is visible at the tip of the needle.
7. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
8. 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.
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, the depth of injection and volume administered may vary based on the subject's treatment needs. A retrograde linear threading technique, serial puncture injections, or a combination of the 2 have been used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or bluish discoloration.
11. Inject Restylane Defyne by applying even pressure on the plunger rod while slowly pulling the needle backward. 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.
12. Injection volume to achieve optimal correction of moderate to severe nasolabial folds is generally about 1.4 mL per treatment site. Injection volume to achieve optimal correction for retreatment is generally about 0.7 mL per treatment site.

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.<sup>1</sup>
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.
18. The health care practitioner should instruct the patient to promptly report any problems associated with the use of Restylane Defyne.

### **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.
- If the treated area is swollen, an ice pack may be applied to the site for a short period.
- To report an adverse reaction, phone Galderma Laboratories, L.P, 1-855-425-8722.

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

## 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 25°C/77°F. 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

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

### **Manufactured for**

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