RHA Redensity® Eye

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA Redensity® Eye, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA Redensity® Eye is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant of both crosslinked and non-crosslinked hyaluronic acid. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using the *streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA Redensity® Eye also contains 0.3% mepivacaine hydrochloride to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA Redensity® Eye is indicated for injection into the sub-dermis and supraperiosteum, for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, in adults aged 22 years or older.

CONTRAINDICATIONS

- RHA Redensity® Eye is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA Redensity® Eye contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- RHA Redensity® Eye should not be used in patients with previous hypersensitivity to local anesthetics of the amide-type, such as mepivacaine or lidocaine.
- RHA Redensity® Eye should not be used in patients with bleeding disorders.

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
  - Do not inject into blood vessels.
  - 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 or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section and the POST-MARKETING SURVEILLANCE section for more details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.
- Do not use pre-hole needle to inject the product.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, 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.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- The safety and effectiveness for the treatment of excessive orbital fat prolapse, excessive lower eyelid skin laxity, extropion or entropion has not been established.
- The safety and effectiveness of cannula injection to correct volume deficiencies of the infraorbital region have only been clinically evaluated with two brands of blunt-tip cannula (SoftFil® Precision and TSK STERiGLIDE™) that were 25G and 1 ½ inches in length.

- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA Redensity® Eye should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA Redensity® Eye injection sites. RHA Redensity® Eye should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA Redensity® Eye into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA Redensity® Eye, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA Redensity® Eye is administered before the skin has healed completely after such a procedure.
- RHA Redensity® Eye is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA Redensity® Eye is packaged for single-use. Do not reuse a syringe after treatment. Do not re-sterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution.
- RHA Redensity® Eye is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REV-NOW (877-373-8669).
- Failure to comply with the needle or cannula attachment instructions could result in needle or cannula disengagement and/or product leakage at the Luer-lock and needle/cannula hub connection.

ADVERSE EXPERIENCES

RHA Redensity® Eye and RHA Redensity® Eye Lido have the same formulation except for a difference in the anesthetic agent: RHA® Redensity® Eye contains mepivacaine (0.3% w/w), while RHA® Redensity® Eye Lido contains lidocaine (0.3% w/w). Mepivacaine and lidocaine have many similar and equivalent physico-chemical characteristics and properties, they are also pharmacologically related.

Due to the similarities in the formulation of RHA Redensity® Eye and RHA Redensity® Eye Lido, the U.S. clinical evaluation of RHA Redensity® Eye Lido supports the indication for the correction of moderate to severe tissue volume deficiencies in the infraorbital region for RHA Redensity® Eye. The U.S. clinical evaluation of RHA Redensity® Eye Lido provides safety and effectiveness information about RHA Redensity® Eye for the infraorbital region indication. The safety information from this study applies to both RHA Redensity® Eye and RHA® Redensity® Eye Lido and are summarized below under "**Clinical Evaluation of RHA Redensity® Eye Lido in the infraorbital region"**.

1. Clinical Evaluation of RHA Redensity® Eye Lido in the infraorbital region

Clinical study TEO-RHA-1902 was a multicenter, controlled, randomized, blinded, No-Treatment control, prospective clinical study designed to compare the safety and effectiveness of RHA Redensity® Eye Lido versus a No-Treatment control for the treatment of moderate to severe tissue volume deficiencies in the infraorbital region. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 30-day diary after each injection.

CTRs are commonly expected injection site responses which are temporally associated with injection of a dermal filler. Events like redness, swelling, pain, bruising, tenderness, and lumps and bumps are examples of expected CTRs. Severe CTRs, or those lasting longer than 30 days or present on the last day of the subject diary, were automatically elevated to an adverse event.

Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:
- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: Some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were tenderness, swelling, bruising, lumps/bumps and firmness.
- Fewer than 1% of subjects still experienced tenderness on the last day of the diary and swelling had resolved in 96.9% of subjects the last

day of the 30-day diary.

- Nearly 20% of subjects did not experience any CTR.
- Nearly 70% of subjects experienced a CTR that lasted 1 to 3 days.
- More than 70% of CTRs had resolved within 7 days.
- On the last day of the diary, only 4.4% of CTRs were still present and a third of those was lumps/bumps. The rates were similar for subjects injected with a cannula or a needle. None were "severe".
- Other than lumps/bumps, each type of CTR that was present on the last day of the diary was present in at most approximately 1 to 3% of subjects.
- For nearly all CTRs (more than 94%), the maximal severity reported was "Mild" or "Moderate".
- Fewer than 5% of subjects experienced a CTR reported as "Severe".
- The most frequent CTR that was reported as "Severe" was bruising when injected with a needle. Less than 2% of subjects still experienced bruising at the end of the 30-Day diary.
- All CTRs which persisted on the last of the diary were deemed "Mild" by the treating investigator.
- The incidence rate of any CTR tended to be higher when injected with a needle (89.1%) than when injected with a cannula (73.5%).
- The incidence rates of redness and bruising were lesser when injected with a cannula (23.0% and 38.1%, respectively) than when injected with a needle (49.1% and 71.8%, respectively).
- The incidence rates by duration were similar between needle and cannula.

Table 1*: *Common Treatment Responses by maximum severity after initial treatment with RHA Redensity® Eye Lido (pooled analysis)– Safety Population

CTR	Severity	Needle	Cannula	Total
Number of subjects		116	117	233
Number of CTR diaries retrieved		110	113	223
At least 1 CTR	None	12 (10.9%)	30 (26.5%)	42 (18.8%)
	Mild	50 (45.5%)	64 (56.6%)	114 (51.1%)
	Moderate	39 (35.5%)	18 (15.9%)	57 (25.6%)
	Severe	9 (8.2%)	1 (0.9%)	10 (4.5%)
Redness	None	56 (50.9%)	87 (77.0%)	143 (64.1%)
	Mild	41 (37.3%)	23 (20.4%)	64 (28.7%)
	Moderate	10 (9.1%)	3 (2.7%)	13 (5.8%)
	Severe	3 (2.7%)	0	3 (1.3%)
Pain	None	89 (80.9%)	92 (81.4%)	181 (81.2%)
	Mild	19 (17.3%)	20 (17.7%)	39 (17.5%)
	Moderate	2 (1.8%)	1 (0.9%)	3 (1.3%)
	Severe	0	0	0
Tenderness	None	50 (45.5%)	45 (39.8%)	95 (42.6%)
	Mild	54 (49.1%)	59 (52.2%)	113 (50.7%)
	Moderate	6 (5.5%)	9 (8.0%)	15 (6.7%)
	Severe	0	0	0
Firmness	None	59 (53.6%)	65 (57.5%)	124 (55.6%)
	Mild	36 (32.7%)	44 (38.9%)	80 (35.9%)
	Moderate	14 (12.7%)	4 (3.5%)	18 (8.1%)
	Severe	1 (0.9%)	0	1 (0.4%)
Swelling	None	37 (33.6%)	59 (52.2%)	96 (43.0%)
	Mild	48 (43.6%)	45 (39.8%)	93 (41.7%)
	Moderate	22 (20.0%)	9 (8.0%)	31 (13.9%)
	Severe	3 (2.7%)	0	3 (1.3%)
Lumps/Bumps	None	50 (45.5%)	63 (55.8%)	113 (50.7%)
	Mild	40 (36.4%)	43 (38.1%)	83 (37.2%)
	Moderate	18 (16.4%)	6 (5.3%)	24 (10.8%)
	Severe	2 (1.8%)	1 (0.9%)	3 (1.3%)
Bruising	None	31 (28.2%)	70 (61.9%)	101 (45.3%)
	Mild	45 (40.9%)	37 (32.7%)	82 (36.8%)
	Moderate	28 (25.5%)	6 (5.3%)	34 (15.2%)

CTR	Severity	Needle	Cannula	Total
	Severe	6 (5.5%)	0	6 (2.7%)
Itching	None	95 (86.4%)	103 (91.2%)	198 (88.8%)
	Mild	14 (12.7%)	9 (8.0%)	23 (10.3%)
	Moderate	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Severe	0	0	0
Discoloration	None	62 (56.4%)	81 (71.7%)	143 (64.1%)
	Mild	31 (28.2%)	29 (25.7%)	60 (26.9%)
	Moderate	14 (12.7%)	3 (2.7%)	17 (7.6%)
	Severe	3 (2.7%)	0	3 (1.3%)

Table 2*: *Common Treatment Responses by total duration after initial treatment with RHA Redensity® Eye Lido (pooled analysis) reported in subject 30-day diary – Safety Population

Total Duration (days)[a]							
CTR after initial injection	**Group**	Subjects Experiencing the **CTR**	**1-3**	**4-7**	**8-14**	**15-30**	**Last Day Diary[b]**
Any CTR	Needle	98 (89.1%)	81 (73.6%)	67 (60.9%)	46 (41.8%)	43 (39.1%)	13 (11.8%)
	Cannula	83 (73.5%)	70 (61.9%)	42 (37.2%)	22 (19.5%)	23 (20.4%)	14 (12.4%)
	Total	181 (81.2%)	151 (67.7%)	109 (48.9%)	68 (30.5%)	66 (29.6%)	27 (12.1%)
Redness	Needle	54 (49.1%)	35 (31.8%)	13 (11.8%)	2 (1.8%)	4 (3.6%)	2 (1.8%)
	Cannula	26 (23.0%)	19 (16.8%)	3 (2.7%)	1 (0.9%)	3 (2.7%)	0
	Total	80 (35.9%)	54 (24.2%)	16 (7.2%)	3 (1.3%)	7 (3.1%)	2 (0.9%)
Pain	Needle	21 (19.1%)	15 (13.6%)	4 (3.6%)	2 (1.8%)	0	0
	Cannula	21 (18.6%)	18 (15.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0
	Total	42 (18.8%)	33 (14.8%)	5 (2.2%)	3 (1.3%)	1 (0.4%)	0
Tenderness	Needle	60 (54.5%)	29 (26.4%)	21 (19.1%)	7 (6.4%)	3 (2.7%)	0
	Cannula	68 (60.2%)	40 (35.4%)	14 (12.4%)	7 (6.2%)	7 (6.2%)	2 (1.8%)
	Total	128 (57.4%)	69 (30.9%)	35 (15.7%)	14 (6.3%)	10 (4.5%)	2 (0.9%)
Firmness	Needle	51 (46.4%)	19 (17.3%)	15 (13.6%)	8 (7.3%)	9 (8.2%)	0
	Cannula	48 (42.5%)	29 (25.7%)	12 (10.6%)	4 (3.5%)	3 (2.7%)	2 (1.8%)
	Total	99 (44.4%)	48 (21.5%)	27 (12.1%)	12 (5.4%)	12 (5.4%)	2 (0.9%)
Swelling	Needle	73 (66.4%)	26 (23.6%)	17 (15.5%)	17 (15.5%)	13 (11.8%)	4 (3.6%)
	Cannula	54 (47.8%)	29 (25.7%)	12 (10.6%)	7 (6.2%)	6 (5.3%)	3 (2.7%)
	Total	127 (57.0%)	55 (24.7%)	29 (13.0%)	24 (10.8%)	19 (8.5%)	7 (3.1%)
Lumps/	Needle	60 (54.5%)	23 (20.9%)	14 (12.7%)	12 (10.9%)	11 (10.0%)	5 (4.5%)
Bumps	Cannula	50 (44.2%)	21 (18.6%)	10 (8.8%)	6 (5.3%)	13 (11.5%)	7 (6.2%)
	Total	110 (49.3%)	44 (19.7%)	24 (10.8%)	18 (8.1%)	24 (10.8%)	12 (5.4%)
Bruising	Needle	79 (71.8%)	6 (5.5%)	32 (29.1%)	22 (20.0%)	19 (17.3%)	2 (1.8%)
	Cannula	43 (38.1%)	17 (15.0%)	12 (10.6%)	11 (9.7%)	3 (2.7%)	2 (1.8%)
	Total	122 (54.7%)	23 (10.3%)	44 (19.7%)	33 (14.8%)	22 (9.9%)	4 (1.8%)
Itching	Needle	15 (13.6%)	9 (8.2%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0
	Cannula	10 (8.8%)	7 (6.2%)	2 (1.8%)	0	1 (0.9%)	0
	Total	25 (11.2%)	16 (7.2%)	6 (2.7%)	1 (0.4%)	2 (0.9%)	0
Discoloration	Needle	48 (43.6%)	14 (12.7%)	12 (10.9%)	10 (9.1%)	12 (10.9%)	4 (3.6%)
	Cannula	32 (28.3%)	14 (12.4%)	8 (7.1%)	4 (3.5%)	6 (5.3%)	3 (2.7%)
	Total	80 (35.9%)	28 (12.6%)	20 (9.0%)	14 (6.3%)	18 (8.1%)	7 (3.1%)

[a] Duration refers to number of days cited in the patient diary, irrespective of the date of injection (maximum duration)
[b] The CTR number indicated in the "Last Day" column are also included in the 15-30 day column

The Tyndall effect (bluish discoloration under the skin caused by blue light spectrum scattered by the colloid particles) was observed in 7 subjects: 5 in the cannula subgroup and 2 in the needle subgroup. All were considered mild and resolved without sequalae.

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- Most treatment-related AEs were mild (93.0%, 53/57) and a few were moderate (7.0%, 4/57) in severity. None were severe.
- Overall, 17.2% (40/233) subjects experienced one treatment-related adverse event.
- Most of treatment-related AEs experienced were typical events following an injection of a hyaluronic acid-based dermal filler. The distribution of the events was similar across treatment with needle or cannula. The 3 most frequent treatment-related AEs were site discoloration, injection site mass and injection site swelling. Other reported treatment-related AEs such as headache and erythema are less typical but not unexpected following a dermal filler injection.
- All treatment-related AEs were temporally associated with a recent injection (no late onset).
- The majority of treatment-related AEs were based on subjects' diary entries (Common Treatment Responses or from a predefined list of events in the diary or reported as "other" in the diary) (77.2%, 44/57) and others were identified by the Treating Investigator during a site visit.
- The duration of treatment-related AEs varied from 1 to 90 days except for five events. Of these 5 treatment-related AEs , the longest duration was 264 days, recorded for a persistent edema of mild severity that resolved without sequelae. This was followed by an event lasting 261 days, a worsening of left eye festoon of mild severity, which also resolved without sequalae. Three additional treatment-related AEs had durations ranging from 97 to 155 days: "bilateral periorbital puffiness" (155 days), "Tyndall effect" (148 days), and "left lateral infraorbital region visible filler product" (97 days), all of mild severity and which resolved without sequelae.
- For the majority of subjects who experienced a treatment-related AE in the needle subgroup (15/22, 68.2%) and for more than a third of subjects in the cannula subgroup (6/18, 33.3%), their treatment-related AEs lasted less than 8 days. For subjects who were injected with the cannula, 50% (9/18) of them experienced a treatment-related AEs for less than 15 days.
- Almost all treatment-related AEs resolved by exit, except 3 ongoing events related to 2 subjects lost-to-follow-up (1 subject with mild Tyndall effect and mild swelling of the lower left eyelid was last seen 71 days after a treatment-related AE was identified and 1 subject with moderate bruising on the left cheek was last seen 13 days after a treatment-related AE was identified).
- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no events of vascular occlusion.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

The incidence rate of treatment- related AE was not different in subjects with higher Fitzpatrick skin types, this was also the case for subjects in the needle and cannula subgroups.

There were no reported cases of scarring, keloid formation or hyperpigmentation.

2. Post-marketing Surveillance

As RHA Redensity® Eye is a product from the RHA family containing mepivacaine it is expected to present a safety profile identical to the other products of RHA family. The following post Marketing Surveillance data are based on Adverse Events from the RHA family of products in and outside of United States.

The following adverse events reported as part of post-marketing surveillance were reported with a prevalence equal or superior to 1 occurrence for 100,000 syringes: skin edema, injection site masses (lumps and bumps), skin swelling, skin induration, vascular complication (such as vessel compression/occlusion), pain, ecchymosis, erythema, skin discoloration and inflammatory reaction.
Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, inflammatory nodules (papules), skin necrosis, granuloma, injection site movement impairment, paraesthesia, skin atrophy, injection site fibrosis, urticaria, device dislocation and injection site extravasation.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

In many cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, antibiotics, anti-histamines, anti-inflammatories, anti-viral, corticosteroids, implant dissolution (hyaluronidase), massage, and vasodilators. Final resolution varies from ongoing to total resolution of the symptoms with or without sequelae.

CLINICAL STUDY

CLINICAL STUDY OF RHA REDENSITY® EYE LIDO

RHA Redensity® Eye is strictly identical to RHA Redensity® Eye Lido except for the small amount of anesthetic medicine: RHA Redensity® Eye contains mepivacaine and RHA Redensity® Eye Lido contains lidocaine. Both anesthetics agents are of the same family with the same mechanisms of effect. RHA Redensity® Eye and RHA Redensity® Eye Lido have the same indication. The long-term safety and effectiveness of RHA Redensity® Eye were evaluated in a clinical study using RHA Redensity® Eye Lido.

The long-term safety and effectiveness of RHA Redensity® Eye Lido for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, was evaluated in a U.S. pivotal clinical study described hereafter.

1. Pivotal Study Design: Clinical Evaluation of RHA Redensity® Eye Lido

A randomized, evaluator blinded, No-Treatment control, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA Redensity® Eye Lido in the U.S..
Subjects were randomly assigned to the RHA Redensity® Eye Lido treatment group or to the No-Treatment control group. The Treating Investigator administered the study device to the infraorbital region with a needle or a cannula. Subjects received initial treatment followed up with safety and effectiveness follow-up visits at 2, 4, 8, 12, 24, 36, and 52 weeks after the treatment and visits at 2, 4 and 12 weeks after repeat treatment. The primary endpoint was at Week 12 after initial treatment. Retreatment was performed with the same administration method as initial treatment (needle or cannula).
Subjects were also offered retreatment at Week 52 and were then followed for 3 months after retreatment or until all Adverse Events (AEs) resolved.

Subjects randomized to the No-Treatment control group received their first treatment after the primary endpoint evaluation (Week 12 after randomization) and then followed the same schedule as the initial treatment group until 52 weeks after treatment and 12 weeks after retreatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of superiority of RHA Redensity® Eye Lido versus the No-Treatment control, in terms of rate of responders (≥ 1-grade difference from pre-treatment in both eyes on the Texoane Infraorbital Hollow Scale [TIOHS]) at 12 weeks after initial injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of infraorbital hollows, TIOHS score. The co-primary endpoint was the analysis of superiority of RHA Redensity® Eye Lido versus the No-Treatment control, in terms of selected questions of the FACE-Q *Appraisal of lower eyelids* domain score, a validated Patient Reported Outcome (PRO) questionnaire evaluated 12 weeks after initial injection.

Secondary effectiveness endpoints included responder rate of TIOHS score as rated by the BLE, the TI and Independent Panel Review (IPR) throughout the study; the responder rate of subjects for both eyes and for one eye with ≥1-grade, ≥2-grade and ≥3-grade improvement on the TIOHDS as assessed by the BLE, the TI and the IPR; Global Aesthetic Improvement (GAI), as assessed by the subject, TI and the BLE; impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the *Appraisal of lower eyelids* domain of the FACE-Q©, subject satisfaction questionnaire and the Periorbital Subject Assessment Questionnaire (PASQ) as assessed by the subjects.

Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments, visual assessment tests and Tyndall effect assessment at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale after each injection.

3. Demographics

A total of 248 subjects (23 to 73 years old) were allocated to RHA Redensity® Eye Lido and No-treatment control groups. 248 subjects were included in the intention-to-treat (ITT) population (pooled population) and a total of 218 subjects received a treatment.
Subjects' demographics are presented in Table 3.

***Table 3:** Demographics (ITT population)*

Number / % of subjects	**RHA Redensity® Eye Lido** N[a]=183		**No-Treatment** N[a]=65	
Age				
Mean (SD)	50.0	(10.65)	48.2	(11.11)
min max	24	73	23	73
Gender				
Female	160	87.4%	60	92.3%
Male	23	12.6%	5	7.7%
Race				
White	152	83.1%	58	89.2%
Black or African American	17	9.3%	5	7.7%

Number / % of subjects	RHA Redensity® Eye Lido N[a]=183		No-Treatment N[a]=65	
Am.Indian/N. Alask.	2	1.1%	1	1.5%
N. Hawaiian/P. Isl.	3	1.6%	0	0.0%
Asian	6	3.3%	0	0.0%
Other	0	0%	0	0.0%
Ethnicity				
Hispanic/Latino	49	26.8%	15	25.8%
Not Hispanic/Latino	130	71.0%	49	72.2%
Fitzpatrick Skin Phototype				
I-III	121	66.1%	43	66.2%
IV-VI	62	33.9%	22	33.8%
V/VI	14	7.7%	5	7.7%

[a] All randomized subjects

4. Treatment Characteristics

The overall total mean volume of RHA Redensity® Eye Lido in both eyes at initial treatment was 1.5 mL. It was 1.7 mL when injected with a needle and 1.3 mL when injected with a cannula. The study protocol allowed a maximum of 1.0 mL per treatment session per eye (2 mL total per session). Nearly half of subjects received retreatment at 52 weeks (47.2%, 110/233). And the average volume injected for retreatment was 0.9 mL for both eyes.

RHA Redensity® Eye Lido was administered from the sub-dermis to the supraperiosteum in the infraorbital hollows using different injection techniques to ensure a satisfactory result of the treatment of volume deficiencies in the infraorbital region. More than 50% of subjects were injected into the supraperiosteum only and a third were injected both in the sub-dermis and supraperiosteum layers.
In general, a retrograde linear threading and multi puncture techniques were used for 82.0% of the subjects treated with RHA Redensity® Eye Lido.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA Redensity® Eye Lido: treatment of RHA Redensity® Eye Lido was superior to No-Treatment. The primary effectiveness endpoint was based on the responder rate as assessed (using the TIOHS) by the BLE at 12 weeks after Baseline. A subject was considered to be a TIOHS responder if he/she presented with a ≥1-grade improvement from pre-treatment (Baseline) on both eyes. There was also a co-primary effectiveness endpoint based on a validated patient-reported outcome (PRO) using a subset of questions of the FACE-Q *Appraisal of lower eyelids* at 12 weeks after Baseline.
To successfully achieve the primary endpoint: 1) the responder rate for subjects with RHA Redensity® Eye Lido must be statistically superior to the responder rate for the No-Treatment control, and; 2) the lower bound of the 2-sided 95% CI of the responder rate for subjects treated with RHA Redensity® Eye Lido must be ≥70% and; 3) the lower bound of the 2-sided 95% CI of the difference between the responder rate for subjects treated with RHA Redensity® Eye Lido and the No-Treatment group must be ≥50%.
For the co-primary endpoint to be met: 1) the modified FACE-Q converted Rash score change from Baseline of subjects treated with RHA Redensity® Eye Lido must be statistically superior to those from the No-Treatment group 2) the lower bound of the 2-sided 95% CI of the mean change from Baseline of the raw score must be ≥3, 3) the lower bound of the 2-sided 95% CI of the difference of the change from Baseline of the converted Rasch score between the RHA Redensity® Eye Lido group and No-Treatment group must be ≥12.

The proportion of responders, showing ≥1-grade improvement on the TIOHS was 79.0% in the treatment group and 9.8% in the No-Treatment group, 12 weeks after initial injection. The results showed that treatment of the infraorbital region with RHA Redensity® Eye was statistically superior to no treatment and clinically significant ((p<0.0001). Results are presented in Table 4. The mean change from Baseline of the raw score of the modified FACE-Q was 4.8 for subjects in the treatment group and -0.6 for subjects in the No-treatment group. And the difference from Baseline of the Rasch converted score was 37.5 in the treatment group and -4.1 in the No-treatment group. At 12 weeks after initial treatment, 80.9% of subjects treated with RHA Redensity® Eye reported improvement in the appearance of their infraorbital region based on the study-specific FACE-Q questionnaire *"Appraisal of lower eyelid module"*, with a mean Rasch converted score increasing from 27.1 at Baseline to 64.6 and with the improvement statistically significant (p<0.0001). Results are presented in Table 4 and Table 5.

Table 4: ***Responder rate assessed by a Blinded Live Evaluator at primary endpoint (Visit 5 - 12 weeks after Baseline)***

TIOHS Responder Rate (BLE)		RHA Redensity® Eye Lido	No-Treatment	P-value[b]
Week 12	**N**[a] (observed cases+imputed)	**183 (173+10)**	**65 (52+13)**	
	Responder	79.0% [72.2-84.5]	9.8% [3.9-22.2]	<0.0001
	Not responder	21.0%	90.2%	
	Difference responder rate (tx – No-tx)	69.3% [58.7-79.8]		

[a] ITT population – BLE assessment – Missing value is imputed using regression method within FCS for multiple imputations
[b] Responder = at least 1-point improvement from Baseline in both eyes.

***Table 5:** Modified FACE-Q change from Baseline assessed by the subject at primary endpoint (Visit 5 – 12 weeks after Baseline)*

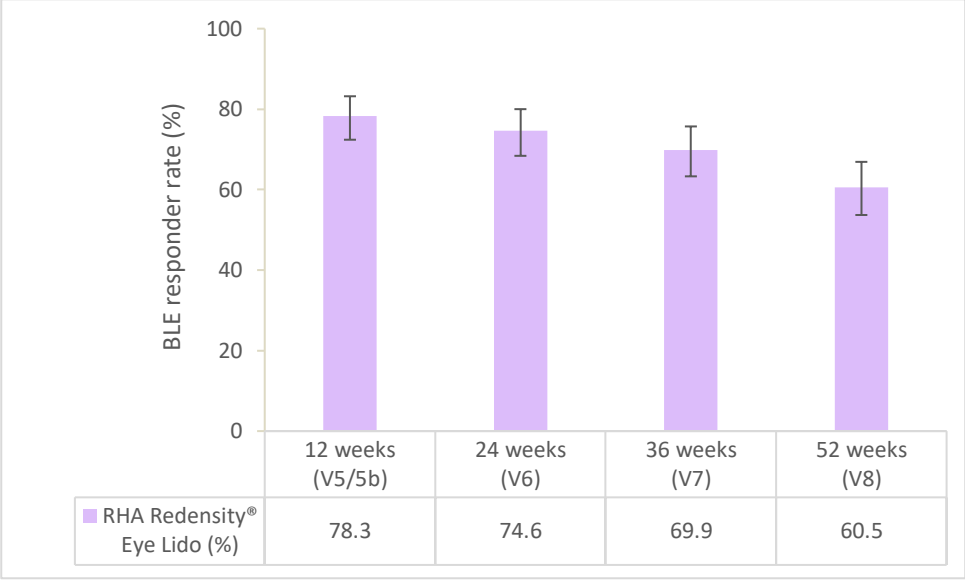
Category		RHA Redensity® Eye Lido	No-Treatment	P-value [b]
	N [a] (observed cases + imputed)	**183 (173+10)**	**65 (52+13)**	
Week 12	Raw score Mean change from baseline 95% CI	7.8 (3.35) [4.2-5.3]	-0.6 (2.09) [-1.2-0.0]	
	Rasch converted Mean change from baseline 95% CI	37.5 (27.04) [33.6-41.5]	-4.1 (17.48) [-8.5,0.2]	<0.0001

[a] ITT population – Missing value is imputed using regression method within FCS for multiple imputations
[b] ANCOVA by treatment arm using baseline modified FACE-Q score and site as covariates

The results demonstrated superiority of RHA Redensity® Eye Lido against No-Treatment control at 12 weeks for the treatment of infraorbital region. In analyses of the pooled population, RHA Redensity® Eye Lido demonstrated marked durability with TIOHS (BLE assessment) responder rates of 74.6%, 69.9% and 60.5% at Weeks 24, 36 and 52, respectively.

Throughout the follow-up period, the aesthetic improvement of the infraorbital region treated with RHA Redensity® Eye Lido continued to be clinically significant (≥ 1-grade difference from pre-treatment on the TIOHS) with 78.3% of subjects at 12 weeks and for more than 60% of the subjects at 52 weeks after initial treatment (Figure 1). There were 31.7% of subjects who presented 2-grades improvement 12 weeks after Baseline and 5.9% with 3-grades improvement.

***Figure 1:** Proportion of responders on Teoxane Infraorbital Hollows Scale (TIOHS) measured by a Blinded Live Evaluator for RHA Redensity® Eye Lido*



On the Global Aesthetic Improvement (GAI) scale, more than 89% of the subjects, TIs and BLEs reported that the infraorbital region treated with RHA Redensity® Eye Lido were improved or very much improved at 12 weeks and this proportion remained greater than 65% up to week 52. In addition, based on the *Appraisal of lower eyelids* domain of the FACE-Q© questionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 54 points from Baseline (Rasch-converted score) throughout the follow-up period. Subjects were asked 7 questions from the FACE-Q *Appraisal of lower eyelids* domain and reported that the treatment with RHA Redensity® Eye Lido was highly effective in reducing concerns related to noticeable lines and wrinkles under the eyes as well as on reducing how old and how tired the eye area made the subject look. Based on the 5-questions of the Periorbital Subject Assessment Questionnaire, subjects indicated a notable improvement in the appearance of the infraorbital region following RHA Redensity® Eye Lido treatment. Key indicators such as looking less tired and old and having smooth, natural and radiant skin, all results showed a marked improvement at 12 weeks post-treatment. By 52 weeks, these improvements were largely sustained.

More than 79% of the subjects reported to be satisfied or very satisfied 12 weeks after initial treatment and the rate of satisfaction remained at more than 64% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

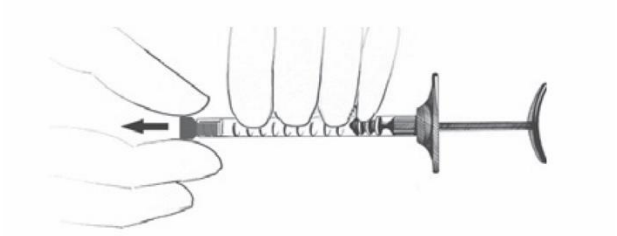
More than 47% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

DIRECTIONS FOR ASSEMBLY OF THE NEEDLE AND CANNULA TO THE SYRINGE

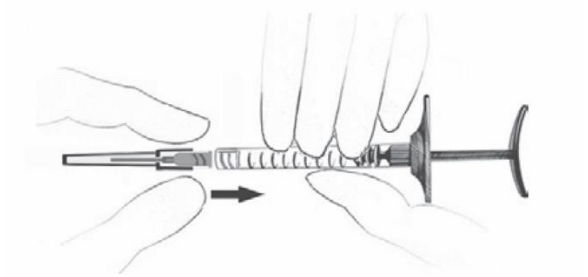
Refer to Figure 2 below (in Section **HOW SUPPLIED**) of the blister and its component to locate the syringe, the 30G ½" needle, the 25G 1 ½" cannula and its pre-hole needle (23G ½").
Follow the steps below to mount the needle or the cannula onto the syringe. If there is any sensation of pressure or obstruction during the injection, the process should be stopped, and the needle/cannula changed.

If using the cannula, before injecting, open the pre-hole needle provided in the packaging with caution, remove the cap and manually use it to create the cannula's entry point.

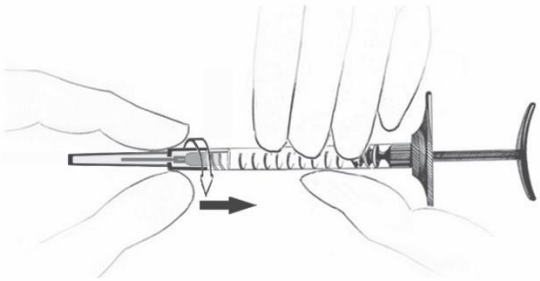
1. While holding the syringe body with one hand, remove the stopper from the syringe by pulling it off with the other hand. Gently tilt back and force carefully until cap disconnects and can be pulled off (seal will be broken). Do not rotate and do not touch the syringe tip to keep it sterile.



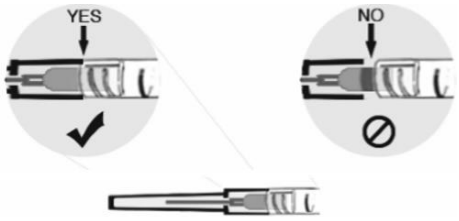
2. Hold the syringe body, and insert the screw thread of the needle/cannula firmly into the syringe end-piece (also called Luer-lock of the syringe).



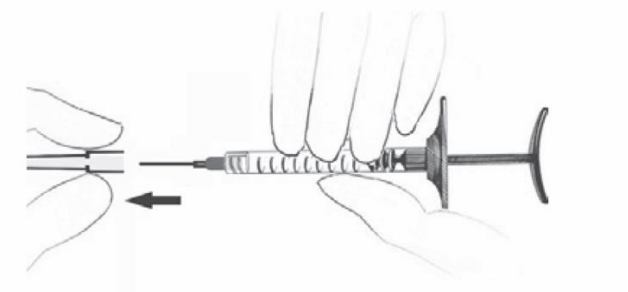
3. Screw the needle/cannula clockwise, while maintaining slight pressure between the needle/cannula and the syringe.



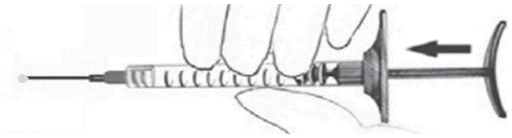
4. Continue screwing until the edge of the cap of the needle/cannula contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle/cannula could be ejected and/or leak at the Luer-lock.



5. Remove the needle's or cannula's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



6. Before injecting, prime the needle or the cannula by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle or cannula.



DIRECTION FOR INJECTIONS

Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

- Ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
- Identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
- Conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

PRE-TREATMENT GUIDELINES

- Prior to treatment (1 week prior), the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, high doses of Vitamin E supplements, anti-coagulants) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment, a thorough clinical exam of the periorbital area should be performed. To test the lower eyelid skin laxity, a snap-back test can be performed. This test is performed by pulling the lower eyelid away from the eye and assessing how quickly and easily the eyelid returns to its normal position. The normal position of the lower eyelid should be reached within 3 seconds.
- Prior to treatment with RHA Redensity® Eye the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- The patient should be in sitting position.
- Sterile gloves are recommended while injecting RHA Redensity® Eye.

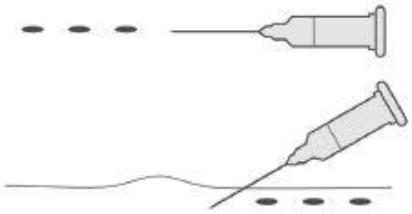
INJECTION TECHNIQUES

- RHA Redensity® Eye can be administered by using a thin gauge needle (30G x ½") (needles brands: TSK PRC, Terumo TW) or with a blunt-tip cannula (25G x 1 ½") (cannula brands: TSK STERiGLIDE™, SoftFil® Precision). Preclinical testing of the syringe with the above needle and cannula brands has confirmed that the interoperability and compatibility are reliable and safe.

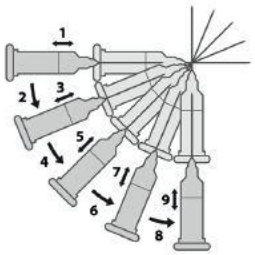
- RHA Redensity® Eye is supplied with one 30G ½" needle and one 25G 1 ½" cannula (and its 23G ½" pre-hole needle).
- When using a needle, the needle is inserted perpendicularly until it touches the periosteum to deposit a small aliquot.
- When using a cannula, an entry point is made in the skin with the pre-hole needle provided with the cannula to create the passage for the cannula with the appropriate depth and direction during injection.
- RHA Redensity® Eye may be administered with a different injection techniques that depend on the injector's experience and preference, and patient characteristics.

A. Serial puncture with a needle (also called multi punctures): consists of multiple bolus injections, evenly and closely spaced. The needle is introduced at 3 different points 1 to 2 mm around the orbital rim below the infraorbital margin (which is free of significant vascular structures). (1) the midway between the medial canthus and the midpupillary line, (2) around the midpupillary line, (3) at lateral canthus line. For each point, the needle is introduced perpendicularly until it touches the periosteum, after which a small aliquot (0.1-0.2 mL) of RHA Redensity® Eye is then **slowly** deposited **with low pressure and bevel down.** Gentle digital massage of the area can also be performed to help to smooth the product into place. If a bruise began to form, the needle should quickly withdraw, and gentle pressure should be applied to the local area with a cotton tip applicator. **If the needle is placed too superficially, visible lumps or bumps of RHA Redensity® Eye would appear. It is also important to avoid overcorrection and depositing large volumes of the filler in one location.** This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.

To treat the palpebromalar grove, inject in a similar fashion with injection points being more lateral.



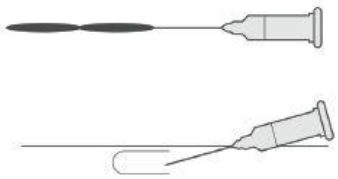
B. Fanning technique: The fanning technique can also be combined with the serial puncture technique. In that case, at the first site injection point, after the introduction of the needle perpendicularly and the deposition of a small aliquot of product at the periosteum. The needle is then retracted 1 to 2 mm, redirected medially, and then advance to touch the periosteum again before depositing another similarly sized **small** aliquot. The needle is never completely withdrawn during the course of medial or lateral movements. These steps are then repeated for the two other points. Gentle digital massage of the area can also be performed to help to smooth the product into place.



C. Linear threading with a needle: the needle is introduced supraperiosteum at the most lateral extent of the tear trough, advancing fully to medial aspect (following the orbital edge) and leaving a **small** amount of product **with low pressure** while the needle is **slowly** withdrawn. Pressure is applied to flatten the injection site. The superior tear trough is then injected in a similar manner all the way to the top of the deformity. Repeated injections (above and below the original injection site) may be required for optimal augmentation.

As for the serial puncture technique, the palpebromalar groove can be treated in a similar fashion with injection point being more lateral.

Whether both areas are injected, for one technique or another, the key element is to make sure that these injections are deep, with the best method to actually hit bone with each subsequent injection to correctly realize that the right plane has been attained.



D. Linear threading with a cannula: an entry hole is made with the pre-hole sharp needle to create the passage for the cannula with the appropriate depth and direction during injection. The entrance point is located in the Suborbicularis oculi fat (SOOF) (about 20 mm below the lateral canthus). This entrance point has been coined as the Redka/Galadari (RG) point and provides for a safe, relatively vascular poor area to inject the tear trough and the palpebromalar groove. The pre-hole needle should be pressed as deep as possible in that area (to at times hitting the periosteum). If this is not performed, then the cannula will meet resistance when introduced.

The cannula is then inserted at pre-incision point and passed into the supraperiosteal plane. The cannula is angled up at about 120 degrees from lateral to medial aspect of the face. The cannula is gently moved on the bone until it reached the inner point of the tear trough. The product is **slowly** deposited **with low pressure** and with a retrograde technique as the cannula is being withdrawn. To check if the cannula is located in a deep layer not as superficial layer, the skin should not be influenced by the cannula's movements.

To treat the palpebromalar groove, and to decrease the risk for potential adverse events (and minimizing bruising), the same entry point used to treat the tear trough deformity can be used. After correcting the tear troughs deformity, without complete withdrawals, the cannula can be pulled laterally to run along the palpebromalar groove and lateral orbital rim to correct that area. The filler should be injected **slowly** deeply into the internal aspect of the orbital septum to create a general increase of volume under the orbicularis oculi muscle.

E. Linear threading anterograde using cannula: threading techniques vary, depending on the area injected and amount of augmentation required. Therea re two ways of product deposition: **retrograde** and **anterograde.**

During a retrograde linear threading injection, the product is **slowly** injected while the cannula is withdrawn.

In an anterograde linear threading technique, the product is **slowly** injected while the cannula is pushed to bone, pushing the surrounding tissues as well as small vessels. After insertion of the cannula, the product is immediately injected, whereas with the retrograde technique, the needle moves forward without injecting the filler.

- RHA Redensity® Eye is injected **slowly** and in small quantities.
- If the color of the needle/cannula can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before withdrawing the needle/cannula from the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the correction to be performed, but it is important to not overcorrect. Based on the U.S. clinical study, patients should be limited to 1.0 mL per treatment per eye (2 mL per session) in the infraorbital region. The safety of injecting greater amounts has not been established.
- Any blanching appearing through the vascular flow 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.
- If the infraorbital hollows need further treatment with RHA Redensity® Eye, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- No massage should be performed in the treated area to prevent displacement of filler from the desired location, except if an overcorrection has occurred. In that case, gentle digital massage is permitted.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- The patient should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least for the first 24 hours, or until initial swelling and redness has resolved.
- The patient should avoid exercise and flight travel for 24 hours after treatment.

STERILE NEEDLES/CANNULAS

- To help avoid needle/cannula breakage, do not attempt to straighten a bent needle/cannula, discard it and complete the procedure with a replacement needle/cannula.

- Do not recap needles or cannulas. Recapping by hand is a hazardous practice and should be avoided.
- RHA Redensity® Eye are provided with 1 needle and 1 cannula (and its pre-hole needle) that do not contain engineered injury protection. Administration of RHA Redensity® Eye requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure, take care to inject in appropriate conditions.
- Obtain prompt medical attention if injury with used needle/cannula occurs.

PATIENT INSTRUCTIONS

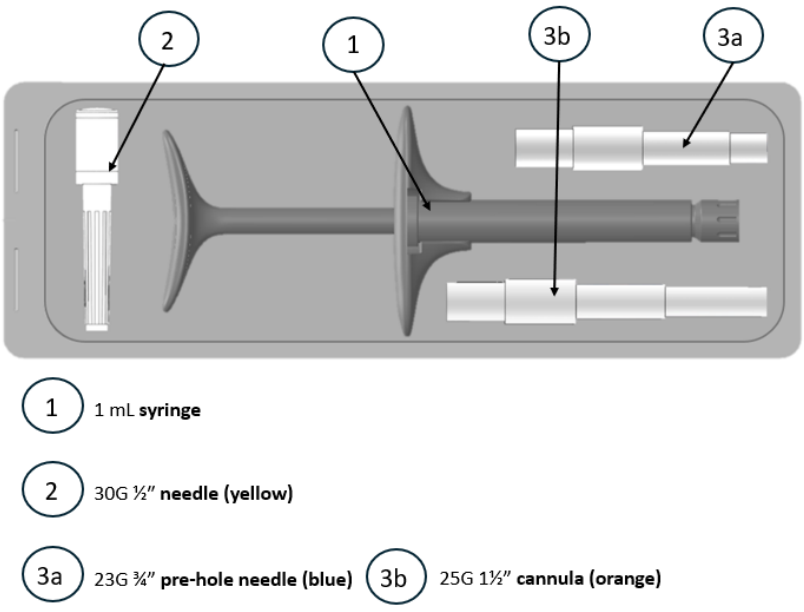
A patient information brochure is available on request, or via the website www.revance.com.
It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up for 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
  - Changes in vision
  - Unusual pain during or shortly after treatment
  - Significant pain away from the injection site
  - Signs of a stroke
  - Any redness and/or visible swelling that lasts for more than a week
  - Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to medical@teoxane.com.

HOW SUPPLIED

RHA Redensity® Eye is supplied in individual blisters containing a 1 mL treatment syringe with one 30G x ½" needle, one 25G x 1 ½" cannula. It also includes a pre-hole needle (23G x ¾") to be used with the cannula as indicated on the carton.

Figure 2: Content of thermoform tray to locate: injection needle, cannula and its pre-hole(*) needle



(*) Cannula pre-hole needle is also called a needle guide or pilot needle

The content of the syringe is sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged.

Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE, STORAGE AND DISPOSAL

RHA Redensity® Eye must be used prior to the expiration date printed on the package.

Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. Do not freeze. Do not store partially used syringes.

After use, needles, cannulas and syringes are potential biohazards.

- Follow Federal, State, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles and cannula in approved sharps containers).
- Disposal of syringes should be in accordance with accepted medical practice and applicable Federal, State and local requirements.

RxOnly

Manufactured by:
TEOXANE SA.
Rue de Lyon, 105
1203 Geneva
Switzerland

Distributed by:
Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA Redensity® is a registered trademark of TEOXANE SA.

US Patent N° 9,353,194; 9,498,562; 9,421,198; 10,786,601; 10,413,637; 11,406,738.

SYMBOLS


Manufacturer's name and address

Catalog number

Lot / batch number


Expiration date (YYYY-MM-DD)


Consult Instructions for use


Single use only

Sterilized using steam (syringe)


Do not use if the package is damaged

RxOnly
Caution: Federal law restricts this device to sale by or on the order of a physician or license practitioner

Sterilize using irradiation (needle)

Sterilized using ethylene oxide (needle)

Caution

TEOXANE

XXXXXX/00 – mm/yyyy

RHA Redensity® Eye Lido

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED PRACTITIONER.

BEFORE USING RHA Redensity® Eye Lido, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY

DEVICE DESCRIPTION

RHA Redensity® Eye Lido is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant of both crosslinked and non-crosslinked hyaluronic acid. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 15 mg/g obtained from bacterial fermentation using the *streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). RHA Redensity® Eye Lido also contains 0.3% lidocaine hydrochloride monohydrate to reduce pain on injection.

INTENDED USE / INDICATIONS

RHA Redensity® Eye Lido is indicated for injection into the sub-dermis and supraperiosteum, for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, in adults aged 22 years or older.

CONTRAINDICATIONS

- RHA Redensity® Eye Lido is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA Redensity® Eye Lido contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA Redensity® Eye Lido should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA Redensity® Eye Lido should not be used in patients with bleeding disorders.

WARNINGS

- Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. To avoid this:
  - Do not inject into blood vessels.
  - 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 or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. If a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure, immediately stop the injection. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives), infection or skin injury is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms (e.g., swelling, redness, tenderness, or pain) and generally resolve within 14 days. Refer to the ADVERSE EXPERIENCES section and the POST-MARKETING SURVEILLANCE section for more details.
- Inflammatory reaction, anaphylactic reaction, edema, implant migration, acne, blisters, scarring, papules and delayed onset of granulomas have been reported following the use of dermal fillers.

PRECAUTIONS

- In order to minimize the risks of potential complications, this product should only be used by experienced health care practitioners who have appropriate training in filler injection techniques, 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.
- The safety and effectiveness for the treatment of anatomic regions other than those described in the INTENDED USE / INDICATIONS section have not been established in controlled clinical studies.
- The safety and effectiveness for the treatment of excessive orbital fat prolapse, excessive lower eyelid skin laxity, extropion or entropion has not been established.
- The safety and effectiveness of cannula injection to correct volume deficiencies of the infraorbital region have only been clinically evaluated with two brands of blunt-tip cannula (SoftFil® Precision and TSK STERiGLIDE™) that were 25G and 1 ½ inches in length.

- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- The safety for use in sites in the presence of other implants (including permanent implants) has not been studied.
- The safety for use during pregnancy, in breastfeeding females, and in patients under 22 years of age has not been established.
- RHA Redensity® Eye Lido should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA Redensity® Eye Lido injection sites. RHA Redensity® Eye Lido should be used with caution in patients who are using substances that can prolong bleeding (such as thrombolytics, anticoagulants, or inhibitors of platelet aggregation).
- Injection of RHA Redensity® Eye Lido into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- If laser treatment, chemical peeling or any other procedure based on active dermal response is considered after treatment with RHA Redensity® Eye Lido, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA Redensity® Eye Lido is administered before the skin has healed completely after such a procedure.
- RHA Redensity® Eye Lido is to be used as supplied. Modification or use of the product outside the Instructions for Use may adversely impact the sterility, safety, homogeneity, or performance of the product.
- RHA Redensity® Eye Lido is packaged for single-use. Do not reuse a syringe after treatment. Do not re-sterilize.
- Do not use if package is opened or damaged. The sterility of the product is not guaranteed in the case of failure to comply with this precaution.
- RHA Redensity® Eye Lido is a clear, colorless gel without particulates. In the event the contents of a syringe show signs of separation and/or appears cloudy, do not use the syringe; contact Revance Therapeutics, Inc. 877-3REVNOW (877-373-8669).
- Failure to comply with the needle or cannula attachment instructions could result in needle /cannula disengagement and/or product leakage at the Luer-lock and needle hub connection.

ADVERSE EXPERIENCES

1. Clinical Evaluation of RHA Redensity® Eye Lido in the infraorbital region

Clinical study TEO-RHA-1902 was a multicenter, controlled, randomized, blinded, No-Treatment control, prospective clinical study designed to compare the safety and effectiveness of RHA Redensity® Eye Lido versus a No-Treatment control for the treatment of moderate to severe tissue volume deficiencies in the infraorbital region. The expected signs and symptoms that occur following the injection of a hyaluronic acid-based dermal filler (i.e., Common Treatment Responses; CTR) were individually assessed by subjects in a preprinted 30-day diary after each injection.

CTRs are commonly expected injection site responses which are temporally associated with injection of a dermal filler. Events like redness, swelling, pain, bruising, tenderness, and lumps and bumps are examples of expected CTRs. Severe CTRs, or those lasting longer than 30 days or present on the last day of the subject diary, were automatically elevated to an adverse event.

Subjects were asked to rate each CTR as None, Mild, Moderate or Severe:
- Mild: Little discomfort, no effect on daily activities, no medication or make-up required
- Moderate: Some discomfort, some effect on daily activities, possibly medication or make-up required
- Severe: Great discomfort, daily activities compromised, very likely medication or make-up required

CTRs by severity and duration are presented respectively, in Table 1 and Table 2.

- The most frequent CTRs were tenderness, swelling, bruising, lumps/bumps and firmness.
- Fewer than 1% of subjects still experienced tenderness on the last day of the diary and swelling had resolved in 96.9% of subjects by the last day of the 30-Day diary.
- Nearly 20% of subjects did not experience any CTR.
- Nearly 70% of subjects experienced a CTR that lasted 1 to 3 days.
- More than 70% of CTRs had resolved within 7 days.
- On the last day of the diary, only 4.4% of CTRs were still present and a third of those was lumps/bumps. The rates were similar for subjects injected with a cannula or a needle. None were “Severe”.
- Other than lumps/bumps, each type of CTR that was present on the last day of the diary was present in at most approximately 1 to 3% of subjects.
- For nearly all CTRs (more than 94%), the maximal severity reported was “Mild” or “Moderate”.
- Fewer than 5% of subjects experienced a CTR reported as “Severe”.

- The most frequent CTR that was reported as "Severe" was bruising when injected with a needle. Less than 2% of subjects still experienced bruising at the end of the 30-Day diary.
- All CTRs which persisted to the last day of the diary were deemed "Mild" by the treating investigator.
- The incidence rate of any CTR tended to be higher when injected with a needle (89.1%) than when injected with a cannula (73.5%).
- The incidence rates of redness and bruising were lesser when injected with a cannula (23.0% and 38.1%, respectively) than when injected with a needle (49.1% and 71.8%, respectively).
- The incidence rates by duration were similar between needle and cannula.

Table 1*: *Common Treatment Responses by maximum severity after initial treatment with RHA Redensity® Eye Lido (pooled analysis)– Safety Population

CTR	Severity	Needle	Cannula	Total
Number of subjects		116	117	233
Number of CTR diaries retrieved		110	113	223
At least 1 CTR	None	12 (10.9%)	30 (26.5%)	42 (18.8%)
	Mild	50 (45.5%)	64 (56.6%)	114 (51.1%)
	Moderate	39 (35.5%)	18 (15.9%)	57 (25.6%)
	Severe	9 (8.2%)	1 (0.9%)	10 (4.5%)
Redness	None	56 (50.9%)	87 (77.0%)	143 (64.1%)
	Mild	41 (37.3%)	23 (20.4%)	64 (28.7%)
	Moderate	10 (9.1%)	3 (2.7%)	13 (5.8%)
	Severe	3 (2.7%)	0	3 (1.3%)
Pain	None	89 (80.9%)	92 (81.4%)	181 (81.2%)
	Mild	19 (17.3%)	20 (17.7%)	39 (17.5%)
	Moderate	2 (1.8%)	1 (0.9%)	3 (1.3%)
	Severe	0	0	0
Tenderness	None	50 (45.5%)	45 (39.8%)	95 (42.6%)
	Mild	54 (49.1%)	59 (52.2%)	113 (50.7%)
	Moderate	6 (5.5%)	9 (8.0%)	15 (6.7%)
	Severe	0	0	0
Firmness	None	59 (53.6%)	65 (57.5%)	124 (55.6%)
	Mild	36 (32.7%)	44 (38.9%)	80 (35.9%)
	Moderate	14 (12.7%)	4 (3.5%)	18 (8.1%)
	Severe	1 (0.9%)	0	1 (0.4%)
Swelling	None	37 (33.6%)	59 (52.2%)	96 (43.0%)
	Mild	48 (43.6%)	45 (39.8%)	93 (41.7%)
	Moderate	22 (20.0%)	9 (8.0%)	31 (13.9%)
	Severe	3 (2.7%)	0	3 (1.3%)
Lumps/Bumps	None	50 (45.5%)	63 (55.8%)	113 (50.7%)
	Mild	40 (36.4%)	43 (38.1%)	83 (37.2%)
	Moderate	18 (16.4%)	6 (5.3%)	24 (10.8%)
	Severe	2 (1.8%)	1 (0.9%)	3 (1.3%)
Bruising	None	31 (28.2%)	70 (61.9%)	101 (45.3%)
	Mild	45 (40.9%)	37 (32.7%)	82 (36.8%)
	Moderate	28 (25.5%)	6 (5.3%)	34 (15.2%)
	Severe	6 (5.5%)	0	6 (2.7%)
Itching	None	95 (86.4%)	103 (91.2%)	198 (88.8%)
	Mild	14 (12.7%)	9 (8.0%)	23 (10.3%)
	Moderate	1 (0.9%)	1 (0.9%)	2 (0.9%)
	Severe	0	0	0
Discoloration	None	62 (56.4%)	81 (71.7%)	143 (64.1%)
	Mild	31 (28.2%)	29 (25.7%)	60 (26.9%)
	Moderate	14 (12.7%)	3 (2.7%)	17 (7.6%)
	Severe	3 (2.7%)	0	3 (1.3%)

Table 2: Common Treatment Responses by total duration after initial treatment with RHA Redensity® Eye Lido (pooled analysis) reported in subject 30-day diary – Safety Population

Total Duration (days)[a]							
CTR after initial injection	**Group**	Subjects Experiencing the **CTR**	**1-3**	**4-7**	**8-14**	**15-30**	**Last Day Diary[b]**
Any CTR	Needle	98 (89.1%)	81 (73.6%)	67 (60.9%)	46 (41.8%)	43 (39.1%)	13 (11.8%)
	Cannula	83 (73.5%)	70 (61.9%)	42 (37.2%)	22 (19.5%)	23 (20.4%)	14 (12.4%)
	Total	181 (81.2%)	151 (67.7%)	109 (48.9%)	68 (30.5%)	66 (29.6%)	27 (12.1%)
Redness	Needle	54 (49.1%)	35 (31.8%)	13 (11.8%)	2 (1.8%)	4 (3.6%)	**2 (1.8**%)
	Cannula	26 (23.0%)	19 (16.8%)	3 (2.7%)	**1** (0.9%)	3 (2.7%)	0
	Total	80 (35.9%)	54 (24.2%)	16 (7.2%)	3 (1.3%)	7 (3.1%)	2 (0.9%)
Pain	Needle	21 (19.1%)	15 (13.6%)	4 (3.6%)	2 (1.8%)	0	0
	Cannula	21 (18.6%)	18 (15.9%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0
	Total	42 (18.8%)	33 (14.8%)	5 (2.2%)	3 (1.3%)	1 (0.4%)	0
Tenderness	Needle	60 (54.5%)	29 (26.4%)	21 (19.1%)	7 (6.4%)	3 (2.7%)	0
	Cannula	68 (60.2%)	40 (35.4%)	14 (12.4%)	7 (6.2%)	7 (6.2%)	2 (1.8%)
	Total	128 (57.4%)	69 (30.9%)	35 (15.7%)	14 (6.3%)	10 (4.5%)	2 (0.9%)
Firmness	Needle	51 (46.4%)	19 (17.3%)	15 (13.6%)	8 (7.3%)	9 (8.2%)	0
	Cannula	48 (42.5%)	29 (25.7%)	12 (10.6%)	4 (3.5%)	**3 (2**.7%)	2 (1.8%)
	Total	99 (44.4%)	48 (21.5%)	27 (12.1%)	12 (5.4%)	12 (5.4%)	2 (0.9%)
Swelling	Needle	73 (66.4%)	26 (23.6%)	17 (15.5%)	17 (15.5%)	13 (11.8%)	4 (3.6%)
	Cannula	54 (47.8%)	29 (25.7%)	12 (10.6%)	7 (6.2%)	6 (5.3%)	3 (2.7%)
	Total	127 (57.0%)	55 (24.7%)	29 (13.0%)	24 (10.8%)	19 (8.5%)	7 (3.1%)
Lumps/	Needle	60 (54.5%)	23 (20.9%)	14 (12.7%)	12 (10.9%)	11 (10.0%)	5 (4.5%)
Bumps	Cannula	50 (44.2%)	21 (18.6%)	10 (8.8%)	6 (5.3%)	13 (11.5%)	7 (6.2%)
	Total	110 (49.3%)	44 (19.7%)	24 (10.8%)	18 (8.1%)	24 (10.8%)	12 (5.4%)
Bruising	Needle	79 (71.8%)	6 (5.5%)	32 (29.1%)	22 (20.0%)	19 (17.3%)	2 (1.8%)
	Cannula	43 (38.1%)	17 (15.0%)	12 (10.6%)	11 (9.7%)	3 (2.7%)	2 (1.8%)
	Total	122 (54.7%)	23 (10.3%)	44 (19.7%)	33 (14.8%)	22 (9.9%)	4 (1.8%)
Itching	Needle	15 (13.6%)	9 (8.2%)	4 (3.6%)	1 (0.9%)	1 (0.9%)	0
	Cannula	10 (8.8%)	7 (6.2%)	2 (1.8%)	0	1 (0.9%)	0
	Total	25 (11.2%)	16 (7.2%)	6 (2.7%)	1 (0.4%)	2 (0.9%)	0
Discoloration	Needle	48 (43.6%)	14 (12.7%)	12 (10.9%)	10 (9.1%)	12 (10.9%)	4 (3.6%)
	Cannula	32 (28.3%)	14 (12.4%)	8 (7.1%)	4 (3.5%)	6 (5.3%)	3 (2.7%)
	Total	80 (35.9%)	28 (12.6%)	20 (9.0%)	14 (6.3%)	18 (8.1%)	7 (3.1%)

[a] Duration refers to number of days cited in the patient diary, irrespective of the date of injection (maximum duration)

[b] The CTR number indicated in the "Last Day" column are also included in the 15-30 day column

The Tyndall effect (bluish discoloration under the skin caused by blue light spectrum scattered by the colloid particles) was observed in 7 subjects: 5 in the cannula subgroup and 2 in the needle subgroup. All were considered mild and resolved without sequalae.

An adverse event (AE) was defined as a treatment-related event that was not considered typical in type and/or duration and/or severity. Also, CTRs from the patient's diary that were recorded on the last day of diary were automatically elevated to the status of adverse event, regardless of severity.

- Most treatment-related AEs were mild (93.0%, 53/57) and a few were moderate (7.0%, 4/57) in severity. None were severe.
- Overall, 17.2% (40/233) subjects experienced one treatment-related adverse event.
- Most of treatment-related AEs experienced were typical events following an injection of a hyaluronic acid-based dermal filler. The distribution of the events was similar across treatment with needle or cannula. The 3 most frequent ADEs were site discoloration, injection site mass and injection site swelling. Other reported treatment-related AEs such as headache and erythema are less typical but not unexpected following a dermal filler injection.
- All treatment-related AEs were temporally associated with a recent injection (no late onset).
- The majority of treatment-related AEs were based on subjects' diary entries (Common Treatment Responses, or from a predefined list of events in the diary or reported as "other" in the diary) (77.2%, 44/57) and others were identified by the Treating Investigator during a site Visit.

- The duration of treatment-related AEs varied from 1 to 90 days except for five events. Of these 5 treatment-related AEs, the longest duration was 264 days, recorded for a persistent edema of mild severity that resolved without sequelae. This was followed by an event lasting 261 days, a worsening of left eye festoon of mild severity, which also resolved without sequelae. Three additional treatment-related AEs had durations ranging from 97 to 155 days: "bilateral periorbital puffiness" (155 days), "Tyndall effect" (148 days), and "left lateral infraorbital region visible filler product" (97 days), all of mild severity and which resolved without sequelae.
- For the majority of subjects who experienced a treatment-related AE in the needle subgroup (15/22, 68.2%) and for more than a third of subjects in the cannula subgroup (6/18, 33.3%), their treatment-related AEs lasted less than 8 days. For subjects who were injected with the cannula, 50% (9/18) of them experienced a treatment-related AE for less than 15 days.
- Almost all treatment-related AEs resolved by exit, except 3 ongoing events related to 2 subjects lost-to-follow-up (1 subject with mild Tyndall effect and mild swelling of the lower left eyelid was last seen 71 days after a treatment-related AE was identified and 1 subject with moderate bruising on the left cheek was last seen 13 days after a treatment-related AE was identified).
- No events were deemed to be a granuloma or delayed inflammatory response.
- There were no events of vascular occlusion
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

The incidence rate of treatment- related AE was not different in subjects with higher Fitzpatrick skin types, this was also the case for subjects in the needle and cannula subgroups.

There were no reported cases of scarring, keloid formation or hyperpigmentation.

2. Post-marketing Surveillance

The following post Marketing Surveillance data are based on adverse events from the RHA family of products in and outside the United States.
The following adverse events reported as part of post-market surveillance data were reported with a prevalence equal or superior to 1 occurrence for 100,000 syringes: skin edema, injection site masses (lumps and bumps), skin swelling, skin induration, vascular complication (such as vessel compression/occlusion), pain, ecchymosis, skin discoloration and inflammatory reaction.
Additionally, other less frequent adverse reactions have also been reported, and include dermal filler overcorrection, allergic reaction, product misplacement, inflammatory nodules (papules), skin necrosis, granuloma, injection site movement impairment/paraesthesia, skin atrophy, injection site fibrosis, urticaria, device discoloration and injection site extravasation.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

In many cases the symptoms resolved without any treatment. Reported treatments and procedures included the use of (in alphabetical order): analgesics, antibiotics, anti-histamines, anti-inflammatories, anti-viral, corticosteroids, implant dissolution (hyaluronidase), massage, and vasodilators. Final resolution varies from ongoing to total resolution of the symptoms with or without sequelae.

CLINICAL STUDY

The safety and effectiveness of RHA® Redensity® Eye Lido for the correction of moderate to severe tissue volume deficiencies in the infraorbital region, was evaluated in a US pivotal clinical study described hereafter.

1. Pivotal Study Design

A randomized, evaluator blinded, No-Treatment control, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA Redensity® Eye Lido in the U.S..
Subjects were randomly assigned to the RHA Redensity® Eye Lido treatment group or to the "No-Treatment" control group. The Treating Investigator administered the study device to infraorbital region with a needle or a cannula. Subjects received initial treatment followed with safety and effectiveness visits at 2, 4, 8, 12, 24, 36, and 52 weeks after the last treatment and 2, 4 and 12 weeks after repeat treatment. The primary endpoint was at Week 12 after initial treatment. Retreatment was performed with the same administration method as initial treatment (needle or cannula).
Subjects were offered retreatment at Week 52 and were then followed for 3 months after retreatment or until all Adverse Events (AEs) resolved.

Subjects randomized to the No-Treatment control group received their first treatment after the primary endpoint evaluation (Week 12 after randomization) and then followed the same schedule as the initial treatment group until 52 weeks after treatment and 12 weeks after retreatment.

2. Study Endpoints

The primary effectiveness endpoint was the analysis of superiority of RHA Redensity® Eye Lido versus the No-Treatment control, in terms of rate of responders (≥ 1-grade difference from pre-treatment in both eyes on the Teoxane Infraorbital Hollow Scale [TIOHS]) at 12 weeks after initial injection, as measured by the Blinded Live Evaluator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of infraorbital hollow, TIOHS score. The co-primary endpoint was the analysis of superiority of RHA Redensity® Eye Lido versus the No-Treatment control, in terms of selected questions of the FACE-Q *Appraisal of lower eyelids* domain score, a validated Patient Reported Outcome (PRO) questionnaire evaluated 12 weeks after initial injection.

Secondary effectiveness endpoints included responder rate of TIOHS score as rated by the BLE, the TI and Independent Panel Review (IPR) throughout the study, the responder rate of subjects for both eyes and for one eye with ≥1-grade, ≥2-grade and ≥3-grade improvement on the TIOHS as assessed by the BLE, the TI and the IPR; Global Aesthetic Improvement (GAI), as assessed by the subject, TI and the BLE; impact and effectiveness of study treatment procedures from the subjects' perspective as assessed by the *Appraisal of lower eyelid*s domain of the FACE-Q©, subject satisfaction questionnaire and a Periorbital Subject Assessment Questionnaire (PSAQ) as assessed by the subjects.

Safety endpoints were evaluated throughout the study, with a 30-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments, visual assessments tests and Tyndall effect assessment at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale after each injection.

3. Demographics

A total of 248 subjects (23 to 73 years old) were allocated to RHA Redensity® Eye Lido and No-treatment control groups. 248 subjects were included in the ITT population (pooled population) and a total of 218 subjects received a treatment.
Subjects' demographics are presented in Table 3.

Table 3*: *Demographics (ITT population)

Number / % of subjects	**RHA Redensity® Eye Lido** N[a]=183		**No-Treatment** N[a]=65	
Age				
Mean (SD)	50.0	(10.65)	48.2	(11.11)
min max	24	73	23	73
Gender				
Female	160	87.4%	60	92.3%
Male	23	12.6%	5	7.7%
Race				
White	152	83.1%	58	89.2%
Black or African American	17	9.3%	5	7.7%
Am.Indian/N. Alask.	2	1.1%	1	1.5%
N. Hawaiian/P. Isl.	3	1.6%	0	0.0%
Asian	6	3.3%	0	0.0%
Other	0	0%	0	0.0%
Ethnicity				
Hispanic/Latino	49	26.8%	15	25.8%
Not Hispanic/Latino	130	71.0%	49	72.2%
Fitzpatrick Skin Phototype				
I-III	121	66.1%	43	66.2%
IV-VI	62	33.9%	22	33.8%
V/VI	14	7.7%	5	7.7%

[a] All randomized subjects

4. Treatment Characteristics

The overall total mean volume of RHA Redensity® Eye Lido injected in both eyes at initial treatment was 1.5 mL. It was 1.7mL when injected with a needle and 1.3 mL when injected with a cannula. The study protocol allowed a maximum of 1.0 mL per treatment session per eye (2 mL total per session). Nearly half of subjects received retreatment at 52 weeks (47.2%, 110/233). And the average volume injected for retreatment was 0.9 mL for both eyes.

RHA Redensity® Eye Lido was administered from the sub-dermis to the supraperiosteum in the infraorbital hollows using different injection techniques to ensure a satisfactory result of the treatment of volume deficiencies in the infraorbital region. More than 50% of subjects were injected into the supraperiosteum only and a third were injected both in the sub-dermis and the supraperiosteum layers.

In general, a retrograde linear threading and multi puncture techniques were used for 82% of the subjects treated with RHA Redensity® Eye Lido.

5. Effectiveness Results

The primary effectiveness endpoint was met for RHA Redensity® Eye Lido: treatment with RHA Redensity® Eye Lido was superior to No-Treatment. The primary effectiveness endpoint was based on the responder rate as assessed (using the TIOHS) by the BLE at 12 weeks after Baseline. A subject was considered to be a TIOHS responder if he/she presented with a ≥1-grade improvement from pre-treatment (Baseline) on both eyes. There was also a co-primary effectiveness endpoint based on a validated patient-reported outcome (PRO) using a subset of questions of the FACE-Q *Appraisal of lower eyelids* at 12 weeks after Baseline.
To successfully achieve the primary endpoint: 1) the responder rate for subjects with RHA Redensity® Eye Lido must be statistically superior to the responder rate for the No-Treatment control, and; 2) the lower bound of the 2-sided 95% CI of the responder rate for subjects treated with RHA Redensity® Eye Lido must be ≥70% and; 3) the lower bound of the 2-sided 95% CI of the difference between the responder rate for subjects treated with RHA Redensity® Eye Lido and the No-Treatment group must be ≥50%.
For the co-primary endpoint to be met: 1) the modified FACE-Q converted Rash score change from Baseline of subjects treated with RHA Redensity® Eye Lido must be statistically superior to those from the No-Treatment group 2) the lower bound of the 2-sided 95% CI of the mean change from Baseline of the raw score for subjects in RHA Redensity® Eye Lido group must be ≥3, 3) the lower bound of the 2-sided 95% CI of the difference of the change from Baseline of the converted Rasch score between the RHA Redensity® Eye Lido group and No-Treatment group must be ≥12.

The proportion of responders, showing ≥1-grade improvement on the TIOHS was 79.0% in the treatment group and 9.8% in the No-Treatment group, 12 weeks after initial injection. The results showed that treatment of the infraorbital region with RHA Redensity® Eye Lido was statistically superior to no treatment and clinically significant ((p<0.0001). Results are presented in Table 4. The mean change from Baseline of the raw score of the modified FACE-Q was 4.8 for subjects in the treatment group and -0.6 for subjects in the No-treatment group. And the difference from baseline of the Rasch converted score was 37.5 in the treatment group and -4.1 in the No-treatment group. At 12 weeks after initial treatment, 80.9% of subjects treated with RHA Redensity® Eye Lido reported improvement in the appearance of their infraorbital region based on the study-specific FACE-Q questionnaire *"Appraisal of lower eyelid module"*, with a mean Rasch converted score increasing from 27.1 at Baseline to 64.6 and with the improvement statistically significant (p<0.0001). Results are presented in Table 4 and Table 5.

Table 4: Responder rate assessed by a Blinded Live Evaluator at primary endpoint (Visit 5 – 12 weeks after Baseline)

TIOHS Responder Rate (BLE)		**RHA Redensity® Eye Lido**	**No-Treatment**	**P-value** [b]
Week 12	**N (observed cases + imputed)** [a]	**183 (173+10)**	**65 (52+13)**	
	Responder	79.0% [72.2-84.5]	9.8% [3.9-22.2]	<0.0001
	Not responder	21.0%	90.2%	
	Difference responder rate (tx – No-tx)	69.3% [58.7-79.8]		

[a] ITT population – BLE assessment – Missing value is imputed using regression method within FCS for multiple imputations
[b] Responder = at least 1-point improvement from Baseline in both eyes.

Table 5: Modified FACE-Q change from Baseline assessed by the subject at primary endpoint (Visit 5 – 12 weeks after Baseline)

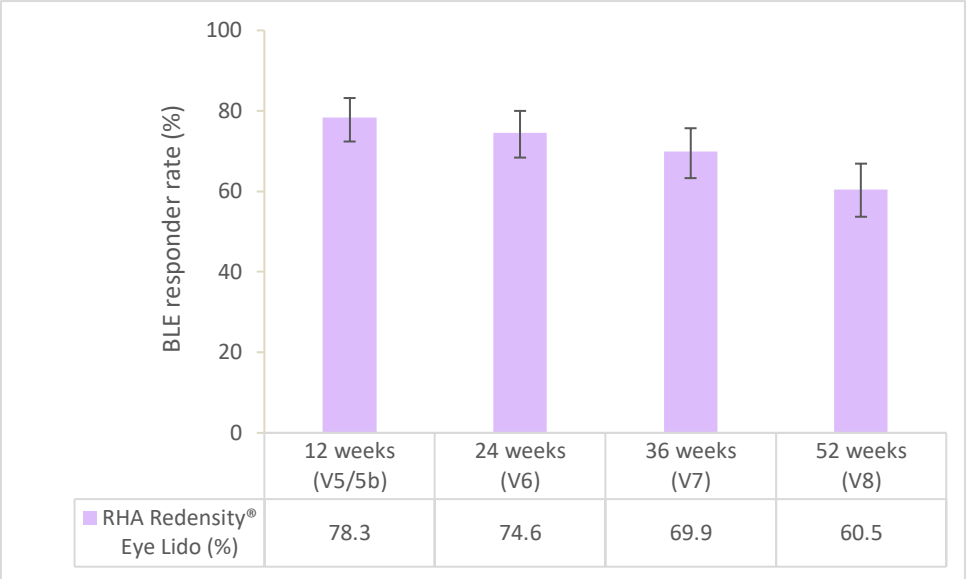
Category		**RHA Redensity® Eye Lido**	**No-Treatment**	**P-value** [b]
Week 12	**N (observed cases + imputed)** [a]	**183 (173+10)**	**65 (52+13)**	
	Raw score Mean change from baseline 95% CI	 7.8 (3.35) [4.2-5.3]	 -0.6 (2.09) [-1.2-0.0]	
	Rasch converted Mean change from baseline 95% CI	 37.5 (27.04) [33.6-41.5]	 -4.1 (17.48) [-8.5,0.2]	<0.0001

[a] ITT population – Missing value is imputed using regression method within FCS for multiple imputations
[b] ANCOVA by treatment arm using baseline modified FACE-Q score and site as covariates

The results demonstrated superiority of RHA Redensity® Eye Lido against No-Treatment control at 12 weeks for the treatment of infraorbital region. In analyses of the pooled population, RHA Redensity® Eye Lido demonstrated marked durability with TIOHS (BLE assessment) responder rates of 74.6%, 69.9% and 60.5% at Weeks 24, 36 and 52, respectively.

Throughout the follow-up period, the aesthetic improvement of the infraorbital region treated with RHA Redensity® Eye Lido continued to be clinically significant (≥ 1-grade difference from pre-treatment on the TIOHS) with 78.3% of subjects at 12 weeks and for more than 60% of the subjects at 52 weeks after initial treatment (Figure 1). There were 31.7% of subjects who presented 2-grades improvement 12 weeks after Baseline and 5.9% with 3-grades improvement.

Figure 1: Proportion of responders on the Teoxane Infraorbital Hollows Scale (TIOHS) measured by a Blinded Live Evaluator for RHA Redensity® Eye Lido



On the Global Aesthetic Improvement (GAI) scale, more than 89% of the subjects, TIs and BLEs reported that the infraorbital region treated with RHA Redensity® Eye Lido were improved or very much improved at 12 weeks and this proportion remained greater than 65% up to Week 52. In addition, based on the *Appraisal of lower eyelids* domain of the FACE-Q© questionnaire, the subjects consistently reported improvement up to 52 weeks with a mean score change of more than 54 points from Baseline (Rasch-converted score) throughout the follow-up period. Subjects were asked 7 questions from the FACE-Q *Appraisal of lower eyelids* domain and reported that the treatment with RHA Redensity® Eye Lido was highly effective in reducing concerns related to noticeable lines and wrinkles under the eyes as well as on reducing how old and how tired the eye area made the subject look. Based on the 5-questions of the Periorbital Subject Assessment Questionnaire, subjects indicated a notable improvement in the appearance of the periorbital region following RHA Redensity® Eye Lido treatment. Key indicators such as looking less tired and old and having smooth, natural and radiant skin, all results showed a marked improvement at 12 weeks post-treatment. By 52 weeks, these improvements were largely sustained.

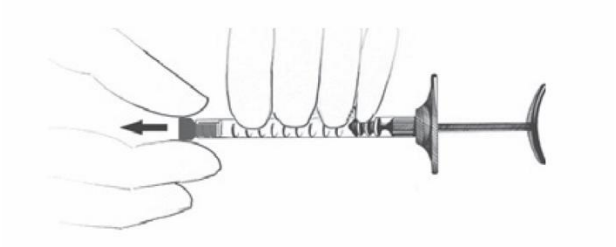
More than 79% of the subjects reported to be satisfied or very satisfied 12 weeks after initial treatment and the rate of satisfaction remained at more than 64% at 52 weeks (the scale grades were: very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied or very dissatisfied).

More than 47% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

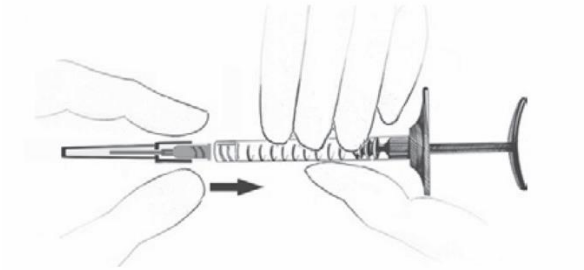
DIRECTIONS FOR ASSEMBLY OF THE NEEDLE AND CANNULA TO THE SYRINGE

Follow the steps below to mount the needle or the cannula onto the syringe. If there is any sensation of pressure or obstruction during the injection, the process should be stopped, and the needle/cannula changed.
If using the cannula, before injecting, open the pre-hole needle provided with the cannula with caution, remove the cap and manually use it to create the cannula's entry point.

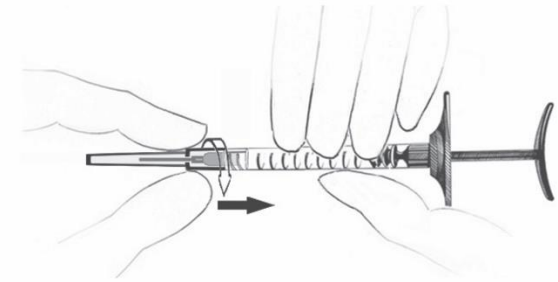
1. While holding the syringe body with one hand, remove the stopper from the syringe by pulling it off with the other hand. Gently tilt back and force carefully until cap disconnects and can be pulled off (seal will be broken). Do not rotate and do not touch the syringe tip to keep it sterile.



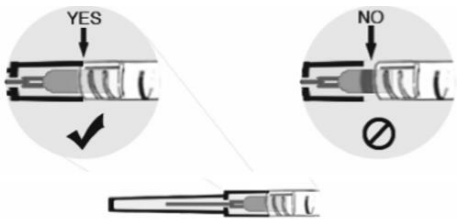
2. Hold the syringe body and insert the screw thread of the needle/cannula firmly into the syringe end-piece (also called Luer-lock of the syringe).



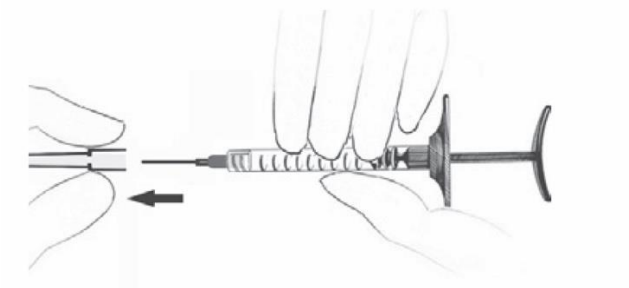
3. Screw the needle clockwise, while maintaining slight pressure between the needle/cannula and the syringe.



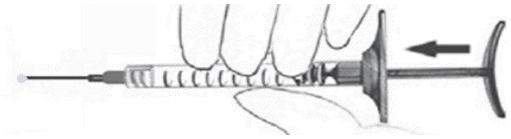
4. Continue screwing until the edge of the cap of the needle/cannula contacts the body of the syringe. There must be no space between these two parts. Failure to follow this instruction means that the needle/cannula could be ejected and/or leak at the Luer-lock.



5. Remove the needle's or cannula's protective cap by pulling it firmly with one hand while holding the body of the syringe with the other.



6. Before injecting, prime the needle or the cannula by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle or cannula.



DIRECTION FOR INJECTIONS

Before and after treatment, health care practitioners are encouraged to conduct vision assessments, including visual acuity, extraocular motility, and visual field testing. Health care practitioners are encouraged to be prepared with the following in the event of an intravascular injection:

- Ensuring supplies are immediately available, as recommended by the American Society for Dermatologic Surgery guidelines
- Identifying a local ophthalmologist or ophthalmology subspecialist to be available in the event of an ophthalmic adverse event related to a dermal filler injection
- Conducting a basic neurologic examination in the event of an ophthalmic adverse event due to the association of such events with central nervous system deficits

PRE-TREATMENT GUIDELINES

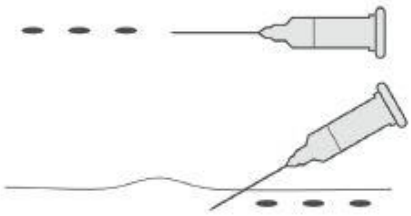
- Prior to treatment (1 week prior), the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, high doses of Vitamin E supplements, anti-coagulants) as these agents may increase bruising and bleeding at the injection site.
- Before starting treatment, a complete medical history should be taken from the patient and the patient should be counseled on appropriate indications, risks, and should be informed about the expected treatment results, and expected responses. The patient should be advised of the necessary precautions before commencing the procedure.
- Prior to treatment, a thorough clinical exam of the periorbital area should be performed. To test the lower eyelid skin laxity, a snap-back test can be performed. This test is performed by pulling the lower eyelid away from the eye and assessing how quickly and easily the eyelid returns to its normal position. The normal position of the lower eyelid should be reached within 3 seconds.
- Prior to treatment with RHA Redensity® Eye Lido the patient should be assessed for appropriate anesthetic treatment for managing comfort (e.g., topical anesthetic, local or nerve block). The patient's face should be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.
- The patient should be in sitting position.
- Sterile gloves are recommended while injecting RHA Redensity® Eye Lido.

INJECTION TECHNIQUES

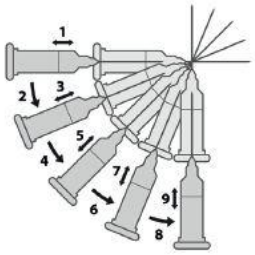
- RHA Redensity® Eye Lido may be administered using a thin gauge needle (30 G x ½") (needles brands: TSK HPC, TSK PRC, Terumo TW, Terumo ETW) or with a blunt-tip cannula (25G x 1 ½") (cannula brands: TSK STERiGLIDE™, SoftFil® Precision). Preclinical testing of the syringe with the above needle and cannula brands has confirmed that the interoperability and compatibility is reliable and safe.
- RHA Redensity® Eye Lido is supplied with two 30G ½" needles. The TSK and SofFil cannulas were used in the clinical trial and are recommended for use with RHA Redensity® Eye Lido (not provided in the packaging).
- When using a needle, the needle is inserted perpendicularly until it touches the periosteum to deposit a small aliquot.
- When using a cannula, an entry hole is made with the pre-hole sharp needle (provided with the cannula) to create the passage for the cannula with the appropriate depth and direction during injection.
- RHA Redensity® Eye Lido can be administered with a number of different injection techniques that depend on the injector's experience and preference, and patient characteristics.

A. Serial puncture with a needle (also called multi-puncture): consists of multiple bolus injections, evenly and closely spaced. The needle is introduced at 3 different points 1 to 2 mm around the orbital rim below the infraorbital margin (which is free of significant vascular structures). (1) the midway between the medial canthus and the midpupillary line, (2) around the midpupillary line, (3) at lateral canthus line. For each point, the needle is introduced perpendicularly until it touches the periosteum, after which a small aliquot (0.1-0.2 mL) of RHA Redensity® Eye Lido is then **slowly** deposited **with low pressure and bevel down.** Gentle digital massage of the area can also be performed to help to smooth the product into place. If a bruise began to form, the needle should quickly withdraw, and gentle pressure should be applied to the local area with a cotton tip applicator. **If the needle is placed too superficially, visible lumps or bumps of RHA Redensity® Eye Lido would appear. It is also important to avoid overcorrection and depositing large volumes of the filler in one location.** This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.

To treat the palpebromalar grove, inject in a similar fashion with injection points being more lateral.



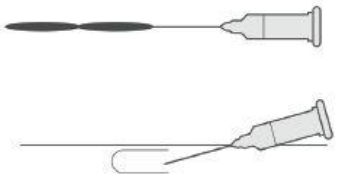
B. **Fanning technique:** The fanning technique can also be combined with the serial puncture technique. In that case, at the first site injection point, after the introduction of the needle perpendicularly and the deposition of a small aliquot of product at the periosteum. The needle is then retracted 1 to 2 mm, redirected medially, and then advance to touch the periosteum again before depositing another similarly sized **small** aliquot. The needle is never completely withdrawn during the course of medial or lateral movements. These steps are then repeated for the two other points. Gentle digital massage of the area can also be performed to help to smooth the product into place.



C. **Linear threading with a needle:** the needle is introduced supraperiosteum at the most lateral extent of the tear trough, advancing fully to medial aspect (following the orbital edge) and leaving a **small** amount of product **with low pressure** while the needle is **slowly** withdrawn. Pressure is applied to flatten the injection site. The superior tear trough is then injected in a similar manner all the way to the top of the deformity. Repeated injections (above and below the original injection site) may be required for optimal augmentation.

As for the serial puncture technique, the palpebromalar groove can be treated in a similar fashion with injection point being more lateral.

Whether both areas are injected, for one technique or another, the key element is to make sure that these injections are deep, with the best method to actually hit bone with each subsequent injection to correctly realize that the right plane has been attained.



D. **Linear threading with a cannula:** an entry hole is made with the pre-hole sharp needle to create the passage for the cannula with the appropriate depth and direction during injection. The entrance point is located in the Suborbicularis oculi fat (SOOF) (about 20 mm below the lateral canthus). This entrance point has been coined as the Redka/Galadari (RG) point and provides for a safe, relatively vascular poor area to inject the tear trough and the palpebromalar groove. The pre-hole needle should be pressed as deep as possible in that area (to at times hitting the periosteum). If this is not performed, then the cannula will meet resistance when introduced.

The cannula is then inserted at pre-incision point and passed into the supraperiosteal plane. The cannula is angled up at about 120 degrees from lateral to medial aspect of the face. The cannula is gently moved on the bone until it reached the inner point of the tear trough. The product is **slowly** deposited **with low pressure** and with a retrograde technique as the cannula is being withdrawn. To check if the cannula is located in a deep layer not as superficial layer, the skin should not be influenced by the cannula's movements.

To treat the palpebromalar groove, and to decrease the risk for potential adverse events (and minimizing bruising), the same entry point used to treat the tear trough deformity can be used. After correcting the tear troughs deformity, without complete withdrawals, the cannula can be pulled laterally to run along the palpebromalar groove and lateral orbital rim to correct that area. The filler should be injected **slowly** deeply into the internal aspect of the orbital septum to create a general increase of volume under the orbicularis oculi muscle.

E. Linear threading anterograde using cannula: threading techniques vary, depending on the area injected and amount of augmentation required. Therea re two ways of product deposition: **retrograde** and **anterograde.**
During a retrograde linear threading injection, the product is **slowly** injected while the cannula is withdrawn.
In an anterograde linear threading technique, the product is **slowly** injected while the cannula is pushed to bone, pushing the surrounding tissues as well as small vessels. After insertion of the cannula, the product is immediately injected, whereas with the retrograde technique, the needle moves forward without injecting the filler.

- RHA Redensity® Eye Lido is injected **slowly** and in small quantities.
- If the color of the needle/cannula can be seen through the skin during injection, this means that the injection is too superficial. This should be avoided as the results of the correction could be irregular.
- The injection should be stopped before withdrawing the needle/cannula from the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the correction to be performed, but it is important to not overcorrect. Based on the U.S. clinical study, patients should be limited to 1.0 mL per treatment per eye (2mL per session) in the infraorbital region. The safety of injecting greater amounts has not been established.
- Any blanching appearing through the vascular flow 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.
- If the infraorbital hollows need further treatment with RHA Redensity® Eye Lido, the same procedure should be repeated until a satisfactory result is obtained.

POST-TREATMENT GUIDELINES

- No massage should be performed in the treated area to prevent displacement of filler from the desired location, except if an overcorrection has occurred. In that case, gentle digital massage is permitted.
- If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period (e.g., 5-10 minutes). Ice should be used with caution if the area is still numb from anesthetic to avoid thermal injury.
- The patient should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least for the first 24 hours, or until initial swelling and redness has resolved.
- The patient should avoid exercise and flight travel for 24 hours after treatment.

STERILE NEEDLES/CANNULAS

- To help avoid needle or cannula breakage, do not attempt to straighten a bent needle or cannula. Discard it and complete the procedure with a replacement needle or cannula.
- Do not recap needles or cannulas. Recapping by hand is a hazardous practice and should be avoided.
- RHA Redensity® Eye Lido is provided with 2 needles that do not contain engineered injury protection. Administration of RHA Redensity® Eye Lido requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. To avoid needle stick injury and sharp exposure take care to inject in appropriate conditions.
- Obtain prompt medical attention if injury with used needle/cannulas occurs.

PATIENT INSTRUCTIONS

A patient information brochure is available on request, or via the website www.revance.com.
It is recommended that the following information be shared with patients:

- Patients should be advised not to wear make-up for 12 hours following injection.
- Patient should be advised not to take high-dose Vitamin E, aspirin, anti-inflammatories or anti-coagulants during the week prior to the injection. Patients must not discontinue such treatment without talking with their prescribing physician.
- Patients should minimize exposure of the treated area to excessive sun, UV lamp exposure and extreme temperatures (e.g. cold weather, sauna) at least within the first 24 hours, or until initial swelling and redness has resolved. Exposure to any of the above may cause/exacerbate and/or extend the duration of temporary redness, swelling, and/or itching at the treatment sites.
- Patients should notify the injector if any of the following occurs:
    - Changes in vision
    - Unusual pain during or shortly after treatment
    - Significant pain away from the injection site
    - Signs of a stroke
    - Any redness and/or visible swelling that lasts for more than a week

- Any side effect other than those described above or that occur weeks or months after injection
- Adverse reactions should be reported to Revance Therapeutics, Inc at 877-3REV-NOW (877-373-8669) and to medical@teoxane.com.

HOW SUPPLIED

RHA Redensity® Eye Lido is supplied in individual blisters containing a 1 mL treatment syringe with two 30G ½" needles as indicated on the carton.

The content of the syringe is sterile and non-pyrogenic. Do not re-sterilize. Do not use if package is opened or damaged.

Each syringe is packaged into a blister with two unique device identifier traceability labels.

SHELF-LIFE AND STORAGE

RHA Redensity® Eye Lido must be used prior to the expiration date printed on the package.

Store at room temperature (up to 25°C/77°F). Do not expose to direct sunlight. Do not freeze. Do not store partially used syringes.

After use, needles, cannulas and syringes are potential biohazards.

- Follow Federal, State, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles and cannula in approved sharps containers).
- Disposal of syringes should be in accordance with accepted medical practice and applicable Federal, State and local requirements.

Manufactured by:

TEOXANE SA.
Rue de Lyon, 105
1203 Geneva
Switzerland

Distributed by:

Revance Therapeutics, Inc.
1222 Demonbreun Street,
Suite 2000
Nashville, Tennessee 37203

RHA Redensity® is a registered trademark of TEOXANE SA.

Under license U.S. Pat. Nos. 8, 450, 475 ; 8,822, 676 ;
9,089 ,517 ; 9,089, 518 ; 9 ,089 ,519 ; 9 ,238,013 ; 9,358, 322.

SYMBOLS

 Manufacturer's name and address

 Catalog number

 Lot / batch number

 Expiration date (YYYY-MM-DD)

 Consult Instructions for use

 Single use only

 Sterilized using steam (syringe)

 Do not use if the package is damaged

RxOnly — Caution: Federal law restricts this device to sale by or on the order of a physician or license practitioner

Sterilize using irradiation (needle)

Sterilized using ethylene oxide (needle)


Caution

XXXXXX/00 – mm/yyyy