

## RHA<sup>®</sup> 2

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

**BEFORE USING RHA<sup>®</sup> 2, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY**

### DEVICE DESCRIPTION

RHA<sup>®</sup> 2 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 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<sup>®</sup> 2 also contains 0.3% lidocaine hydrochloride to reduce pain on injection.

### INTENDED USE / INDICATIONS

RHA<sup>®</sup> 2 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

### CONTRAINDICATIONS

- RHA<sup>®</sup> 2 is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA<sup>®</sup> 2 contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA<sup>®</sup> 2 should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA<sup>®</sup> 2 should not be used in patients with bleeding disorders.

### WARNINGS

- RHA<sup>®</sup> 2 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at 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 for 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.
- 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<sup>®</sup> 2 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA<sup>®</sup> 2 injection sites. RHA<sup>®</sup> 2 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<sup>®</sup> 2 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<sup>®</sup> 2, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA<sup>®</sup> 2 is administered before the skin has healed completely after such a procedure.
- RHA<sup>®</sup> 2 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<sup>®</sup> 2 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- 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. Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.
- RHA<sup>®</sup> 2 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 TEOXANE US Distributor at (000) 000-0000.

**ADVERSE EXPERIENCES**

**1. Clinical Evaluation of RHA<sup>®</sup> 2**

A multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study compared the safety of RHA<sup>®</sup> 2 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. 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 14-day diary after each injection.

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 firmness, redness, tenderness, swelling, lumps/bumps, and bruising.
- Proportions of subjects experiencing at least one CTR of each category were similar between RHA<sup>®</sup> 2 and control treatment.
- More than 70% of the CTRs had resolved by Day 7.
- The vast majority (more than 85%) of CTRs had resolved by Day 14.
- There were no notable differences between RHA<sup>®</sup> 2 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
- For nearly all CTRs (more than 93%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was “Mild” or “Moderate”.
- On the last day of the diary, nearly all ongoing CTRs had improved to mild.

**Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA<sup>®</sup> 2 and the control device – Safety Population**

Common Treatment Responses	TOTALS		RHA <sup>®</sup> 2 (N <sup>a</sup> =72 NLF)			Control Device (N <sup>a</sup> =72 NLF)		
	RHA <sup>®</sup> 2 n <sup>b</sup> %	CTRL <sup>c</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %
Bruising	36 50.0%	41 56.9%	15 20.8%	16 22.2%	5 6.9%	23 31.9%	9 12.5%	9 12.5%
Discoloration	24 33.3%	27 37.5%	12 16.7%	7 9.7%	5 6.9%	14 19.4%	8 11.1%	5 6.9%
Firmness	46 63.9%	48 66.7%	23 31.9%	20 27.8%	3 4.2%	27 37.5%	20 27.8%	1 1.4%
Itching	12 16.7%	15 20.8%	9 12.5%	3 4.2%	0 0.0%	10 13.9%	4 5.6%	1 1.4%
Lumps/Bumps	38 52.8%	37 51.4%	21 29.2%	14 19.4%	3 4.2%	22 30.6%	13 18.1%	2 2.8%
Pain	19 26.4%	16 22.2%	13 18.1%	6 8.3%	0 0.0%	11 15.3%	5 6.9%	0 0.0%
Redness	45 62.5%	49 68.1%	31 43.1%	13 18.1%	1 1.4%	36 50.0%	11 15.3%	2 2.8%
Swelling	42 58.3%	45 62.5%	27 37.5%	13 18.1%	2 2.8%	31 43.1%	13 18.1%	1 1.4%
Tenderness	44 61.1%	40 55.6%	34 47.2%	10 13.9%	0 0.0%	31 43.1%	9 12.5%	0 0.0%

<sup>a</sup> Number of subjects' NLF treated with the respective device

<sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response

<sup>c</sup> CTRL = Control treatment

<sup>d</sup> Mod = Moderate

**Table 2. Duration of Common Treatment Responses after initial treatment with RHA<sup>®</sup> 2 and the control device – Safety Population**

Common Treatment Responses	RHA <sup>®</sup> 2 (N <sup>a</sup> =72 NLF) N <sup>b</sup> %				Control Device (N <sup>a</sup> =72 NLF) N <sup>b</sup> %			
	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>
Bruising	7 9.7%	13 18.1%	16 22.2%	4 5.6%	10 13.9%	16 22.2%	15 20.8%	3 4.2%
Discoloration	11 15.3%	4 5.6%	9 12.5%	3 4.2%	11.1%	10 13.9%	9 12.5%	3 4.2%
Firmness	13 18.1%	11 15.3%	22 30.6%	14 19.4%	16 22.2%	13 18.1%	19 26.4%	12 16.7%
Itching	5 6.9%	4 5.6%	3 4.2%	3 4.2%	9 12.5%	2 2.8%	4 5.6%	3 4.2%
Lumps/Bumps	11 15.3%	13 18.1%	14 19.4%	12 16.7%	14 19.4%	11 15.3%	12 16.7%	6 8.3%
Pain	11 15.3%	4 5.6%	4 5.6%	3 4.2%	7 9.7%	5 6.9%	4 5.6%	2 2.8%
Redness	28 38.9%	13 18.1%	4 5.6%	1 1.4%	29 40.3%	14 19.4%	6 8.3%	3 4.2%
Swelling	19 26.4%	11 15.3%	12 16.7%	5 6.9%	22 30.6%	15 20.8%	8 11.1%	3 4.2%
Tenderness	23 31.9%	9 12.5%	12 16.7%	5 6.9%	21 29.2%	10 13.9%	9 12.5%	1 1.4%

<sup>a</sup> Number of subject's NLF treated with the respective device

<sup>b</sup> Number of subject's NLF with each specific CTR by maximum duration

<sup>c</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

<sup>d</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

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.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA<sup>®</sup> 2 or control treatment) injection.
- All treatment-related AEs were based on subjects' diary entries (CTRs) except one (injection site bruising; mild) that was reported by the Treating Investigator at time of initial injection and which resolved in 12 days.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

**2. Post-marketing Surveillance**

The following adverse events were reported as part of post-marketing surveillance on the use of RHA<sup>®</sup> 2 outside the United States. These adverse events are listed in order of prevalence: inflammatory reaction, lumps and bumps, edema, vascular complication, acne, blister, bruising, pain, firmness, unsatisfactory result and necrosis.

In some cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): analgesics, aloe vera, antibiotics, antihistamines, anti-viral, drainage, hyaluronidase, massage, NSAIDs, steroids and vasodilators. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

## CLINICAL STUDY

The safety and effectiveness of RHA<sup>®</sup> 2 in the correction of moderate to severe facial wrinkles and folds was evaluated in a US pivotal clinical study described hereafter.

### 1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA<sup>®</sup> 2.

Subjects were randomly assigned to receive RHA<sup>®</sup> 2 and a control treatment in mid-to-deep dermis for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly.

If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.

Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolved. Retreatment on either side was provided using RHA<sup>®</sup> 2 (the control treatment was not used).

Subjects randomized to the “no treatment” control group did not receive treatment.

### 2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA<sup>®</sup> 2 versus the control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Investigator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score.

Secondary effectiveness endpoints included rates of responders ( $\geq 1$  grade difference from pre-treatment on the WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects’ perspective as assessed by the nasolabial fold domain of the FACE-Q<sup>®</sup>, and subject satisfaction. Safety endpoints were evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit. Injection site pain was self-assessed by the subject using a 100mm Visual Analog Scale.

### 3. Demographics

A total of 74 subjects (34 to 79 years old) were allocated to RHA<sup>®</sup> 2 and control treatment, and 26 were allocated to untreated controls. 73 subjects were included in the ITT population.

Subjects’ demographics are presented in Table 3.

**Table 3. Demographics**

Number / % of subjects	RHA <sup>®</sup> 2 versus Control device N <sup>a</sup> =73	
<b>Age</b>		
Mean (SD)	55.5	(10.9)
min max	34	79
<b>Gender</b>		
Female	62	84.9%
Male	11	15.1%
<b>Race</b>		
Caucasian	59	80.8%
Black	9	12.3%
Am.Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	2	2.7%
Other	3	4.1%
<b>Ethnicity</b>		
Hispanic/Latino	21	28.8%
Not Hispanic/Latino	52	71.2%
<b>Fitzpatrick Skin Phototype</b>		
I	1	1.4%
II	24	32.9%
III	20	27.4%
IV	17	23.3%
V	7	9.6%
VI	4	5.5%

<sup>a</sup> Number of subjects in the ITT populations

### 4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total median volume of RHA<sup>®</sup> 2 injected to achieve optimal correction results was 1.4 mL. The proportion of subjects who received touch-up treatment with RHA<sup>®</sup> 2 at Week 2 was 64.4%.

In general, a linear threading or fan-like technique, or combination, was used for 91.0% of the subjects treated with RHA<sup>®</sup> 2.

### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA<sup>®</sup> 2. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA<sup>®</sup> 2 compared to the improvement from pre-injection of the NLF treated with the control treatment, as assessed (using the WSRS) by the BLE at 24 weeks after baseline; results are presented in Table 4.

**Table 4. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study**

	n <sup>a</sup>	RHA <sup>®</sup> 2		Control Device	
		WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>	WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>
Pre-treatment	67	3.45	-	3.45	-
Week 24 <sup>d</sup>	67	2.28	1.16	2.31	1.13
Week 36	65	2.32	1.12	2.32	1.12
Week 52	62	2.37	1.06	2.37	1.06
Week 64	47	2.45	0.94	2.38	1.00

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits

<sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

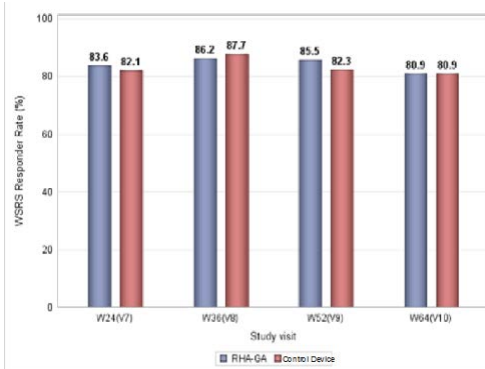
<sup>c</sup> Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

<sup>d</sup> Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA<sup>®</sup> 2 at 24 weeks for the treatment of NLFs. Results also showed that RHA<sup>®</sup> 2 was non-inferior to the control treatment at all study visits.

Throughout the follow-up period, the aesthetic improvement of the RHA<sup>®</sup> 2 treated NLF continued to be clinically significant ( $\geq 1$  grade difference from pre-treatment on the WSRS) for more than 80% of the subjects at 64 weeks after initial treatment (Figure 1).

**Figure 1. Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA<sup>®</sup> 2 and the Control Device**



	Week 24	Week 36	Week 52	Week 64
RHA <sup>®</sup> 2	83.6%	86.2%	85.5%	80.9%
Control Device	82.1%	87.7%	82.3%	80.9%

PP populations at the respective follow-up visits

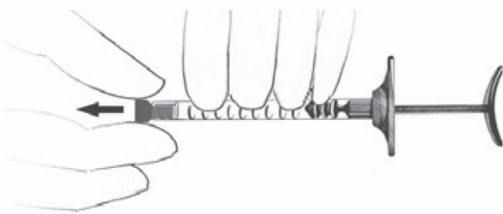
Rate of responders:  $\geq 1$  grade difference from pre-treatment on the WSRS

On the Global Aesthetic Improvement (GAI) scale, more than 84% of the subjects and the BLEs reported that the NLF treated with RHA<sup>®</sup> 2 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q<sup>®</sup> questionnaire with the mean score improving from 24 to more than 60 throughout the follow-up period. More than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained at more than 86% at 64 weeks.

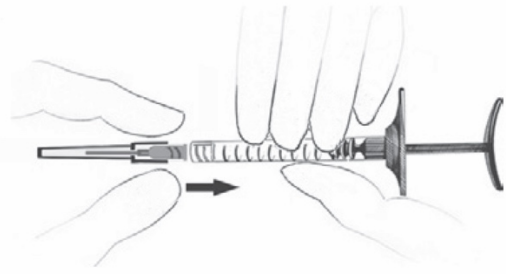
More than 78% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

#### **DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE**

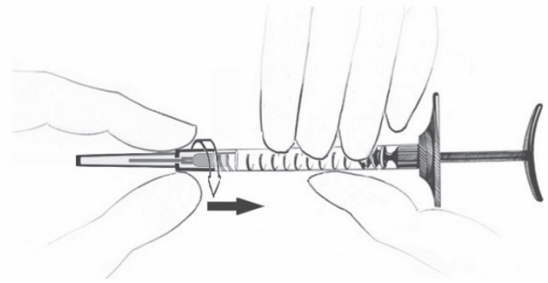
1. Remove the stopper from the syringe by pulling it off.



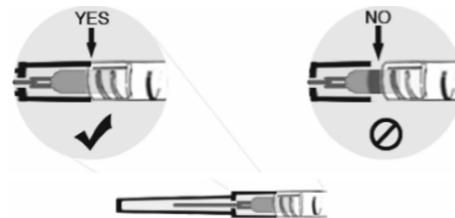
2. Insert the screw thread of the needle firmly into the syringe end-piece.



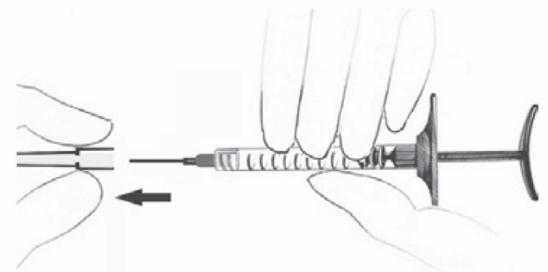
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



#### **PRE-TREATMENT GUIDELINES**

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) 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 with RHA<sup>®</sup> 2 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

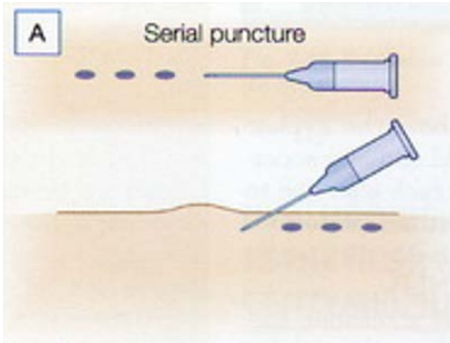
be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.

- Sterile gloves are recommended while injecting RHA<sup>®</sup> 2.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

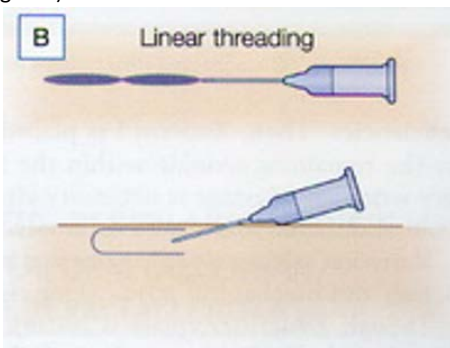
### INJECTION TECHNIQUES

- RHA<sup>®</sup> 2 is administered by using a thin gauge needle (30 G x ½"). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA 2 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

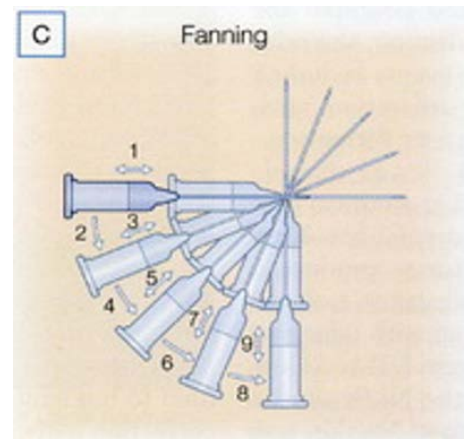
**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



**B. Linear threading:** the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



**C. Fanning technique:** the needle is introduced as for the *Linear threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA<sup>®</sup> 2 is injected slowly into the mid-to-deep dermis. If the injection is made too deeply, i.e. into sub-cutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue does not offer any resistance to product injection, unlike the dermis.
- If the color of the needle 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 pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0mL per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles need further treatment with RHA<sup>®</sup> 2, the same procedure should be repeated until a satisfactory result is obtained.

### POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- 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.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

### STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).

- Obtain prompt medical attention if injury with used needle occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA<sup>®</sup> 2 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA<sup>®</sup> 2 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

#### **PATIENT INSTRUCTIONS**

Patient information brochure is available on request, or via the website [www.teoxane-us-distributor.com](http://www.teoxane-us-distributor.com).

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

- Patients should be advised not to wear make-up during 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 Teoxane US Distributor at (000) 000-0000.

#### **HOW SUPPLIED**

RHA<sup>®</sup> 2 is supplied in individual blisters containing a 1mL treatment syringe with two 30 G x ½” needles as indicated on the carton.

The content of the syringe is sterile and non-pyrogenic. Do not resterilize. 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<sup>®</sup> 2 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.

#### **Manufactured by:**

TEOXANE SA.  
Rue de Lyon, 105  
1203 Geneva  
Switzerland

#### **Distributed by:**

Teoxane US Distributor  
Address  
City, State, Zip Code  
U.S.A.

RHA<sup>®</sup> is a registered trademark of TEOXANE SA.

#### **SYMBOLS**



Manufacturer's name and address



Catalogue number



Lot / batch number



Expiration date (YYYY-MM-DD)



Consult Instructions for use



Single use only



Sterilized using steam



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

## RHA<sup>®</sup> 3

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

**BEFORE USING RHA<sup>®</sup> 3, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY**

### DEVICE DESCRIPTION

RHA<sup>®</sup> 3 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 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<sup>®</sup> 3 also contains 0.3% lidocaine hydrochloride to reduce pain on injection.

### INTENDED USE / INDICATIONS

RHA<sup>®</sup> 3 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

### CONTRAINDICATIONS

- RHA<sup>®</sup> 3 is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA<sup>®</sup> 3 contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA<sup>®</sup> 3 should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA<sup>®</sup> 3 should not be used in patients with bleeding disorders.

### WARNINGS

- RHA<sup>®</sup> 3 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at 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 for details.

- Inflammatory reaction, swelling, edema, ecchymosis, pain, acne, blister, papule and necrosis 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.
- 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<sup>®</sup> 3 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA<sup>®</sup> 3 injection sites. RHA<sup>®</sup> 3 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<sup>®</sup> 3 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<sup>®</sup> 3, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA<sup>®</sup> 3 is administered before the skin has healed completely after such a procedure.
- RHA<sup>®</sup> 3 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<sup>®</sup> 3 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- 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. Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.
- RHA<sup>®</sup> 3 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 TEOXANE US Distributor at (000) 000-0000.

**ADVERSE EXPERIENCES**

**1. Clinical Evaluation of RHA<sup>®</sup> 3**

A multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study compared the safety of RHA<sup>®</sup> 3 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. 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 14-day diary after each injection.

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

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

- The most frequent CTRs were firmness, redness, tenderness, swelling, lumps/bumps, and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA<sup>®</sup> 3 and control treatment.
- More than 60% of the CTRs had resolved by Day 7.
- The majority (more than 88%) of CTRs had resolved by Day 14.
- There were no notable differences between RHA<sup>®</sup> 3 and control treatment with regard to the small proportion of subjects who reported a severe CTR.
- For the majority of CTRs (more than 84%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".
- On the last day of the diary, nearly all ongoing CTR had improved to mild.

**Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA<sup>®</sup> 3 and the Control Device – Safety Population**

Common Treatment Responses	TOTALS		RHA <sup>®</sup> 3 (N <sup>a</sup> =75 NLF)			Control Device (N <sup>a</sup> =75 NLF)		
	RHA <sup>®</sup> 3 n <sup>b</sup> %	CTRL <sup>c</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %
Bruising	42 56.0%	38 50.7%	20 26.7%	15 20.0%	7 9.3%	12 16.0%	20 26.7%	6 8.0%
Discoloration	22 29.3%	22 29.3%	7 9.3%	11 14.7%	4 5.3%	10 13.3%	8 10.7%	4 5.3%
Firmness	48 64.0%	45 60.0%	21 28.0%	21 28.0%	6 8.0%	22 29.3%	21 28.0%	2 2.7%
Itching	13 17.3%	11 14.7%	7 9.3%	4 5.3%	2 2.7%	5 6.7%	4 5.3%	2 2.7%
Lumps/Bumps	49 65.3%	40 53.3%	21 28.0%	21 28.0%	7 9.3%	22 29.3%	14 18.7%	4 5.3%
Pain	30 40.0%	23 30.7%	21 28.0%	6 8.0%	3 4.0%	18 24.0%	4 5.3%	1 1.3%
Redness	43 57.3%	42 56.0%	26 34.7%	14 18.7%	3 4.0%	26 34.7%	15 20.0%	1 1.3%
Swelling	41 54.7%	38 50.7%	22 29.3%	15 20.0%	4 5.3%	22 29.3%	15 20.0%	1 1.3%
Tenderness	44 58.7%	37 49.3%	29 38.7%	12 16.0%	3 4.0%	26 34.7%	10 13.3%	1 1.3%

<sup>a</sup> Number of subjects' NLF treated with the respective device

<sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response

<sup>c</sup> CTRL = Control treatment

<sup>d</sup> Mod = Moderate

**Table 2. Duration of Common Treatment Responses after initial treatment with RHA<sup>®</sup> 3 and the Control Device – Safety Population**

Common Treatment Responses	RHA <sup>®</sup> 3 (N <sup>a</sup> =75 NLF)				Control Device (N <sup>a</sup> =75 NLF)			
	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>
Bruising	11 14.7%	19 25.3%	12 16.0%	4 5.3%	11 14.7%	16 21.3%	11 14.7%	1 1.3%
Discoloration	10 13.3%	6 8.0%	6 8.0%	4 5.3%	13 17.3%	5 6.7%	4 5.3%	3 4.0%
Firmness	18 24.0%	7 9.3%	23 30.7%	9 12.0%	16 21.3%	14 18.7%	15 20.0%	3 4.0%
Itching	9 12.0%	4 5.3%	0 0.0%	0 0.0%	8 10.7%	3 4.0%	0 0.0%	0 0.0%
Lumps/Bumps	17 22.7%	11 14.7%	21 28.0%	12 16.0%	15 20.0%	13 17.3%	12 16.0%	6 8.0%
Pain	21 28.0%	7 9.3%	2 2.7%	0 0.0%	18 24.0%	3 4.0%	2 2.7%	1 1.3%
Redness	27 36.0%	9 12.0%	7 9.3%	2 2.7%	27 36.0%	10 13.3%	5 6.7%	2 2.7%
Swelling	18 24.0%	12 16.0%	11 14.7%	5 6.7%	19 25.3%	11 14.7%	8 10.7%	4 5.3%
Tenderness	17 22.7%	13 17.3%	14 18.7%	5 6.7%	17 22.7%	13 17.3%	7 9.3%	3 4.0%

<sup>a</sup> Number of subject NLF treated with the respective device

<sup>b</sup> Number of subject NLF with each specific CTR by maximum duration

<sup>c</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

<sup>d</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

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.

- All treatment-related AEs were mild or moderate in severity.
- All treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a hyaluronic acid-based dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA<sup>®</sup> 3 or control treatment) injection.
- All treatment-related AEs were based on subjects' diary entries.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

**2. Post-marketing Surveillance**

The following adverse events were reported as part of post-marketing surveillance on the use of RHA<sup>®</sup> 3 outside the US. These adverse events are listed in order of prevalence: anaphylactic reaction, lumps and bumps, papule, granuloma, firmness, implant migration, unsatisfactory results and scarring.

In some cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): hyaluronidase and monitoring at the hospital. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.



## CLINICAL STUDY

The safety and effectiveness of RHA<sup>®</sup> 3 in the correction of moderate to severe facial wrinkles and folds was evaluated in a US pivotal clinical study described hereafter.

### 1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA<sup>®</sup> 3.

Subjects were randomly assigned to receive RHA<sup>®</sup> 3 and control treatment in mid-to-deep dermis for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly.

If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment.

Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolve. Retreatment on either side was provided using RHA<sup>®</sup> 3 (the control treatment was not used).

Subjects randomized to the “no treatment” control group did not receive treatment.

### 2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA<sup>®</sup> 3 versus the control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by a Blinded Live Investigator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score).

Secondary effectiveness endpoints included rates of responders ( $\geq 1$  grade difference from pre-treatment on the WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects’ perspective as assessed by the nasolabial fold domain of the FACE-Q<sup>®</sup>, and subject satisfaction. Safety endpoints was evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

### 3. Demographics

A total of 74 subjects (26 to 77 years old) were allocated to RHA<sup>®</sup> 3 and control treatment, and 26 were allocated to untreated controls. 74 subjects were included in the ITT population.

Subjects’ demographics are presented in Table 3.

**Table 3. Demographics**

Number / % of subjects	RHA <sup>®</sup> 3 versus Control Device N <sup>a</sup> =74	
<b>Age</b>		
Mean (SD)	55.7	(9.4)
min max	26	77
<b>Gender</b>		
Female	68	91.9%
Male	6	8.1%
<b>Race</b>		
Caucasian	62	83.8%
Black	7	9.5%
Am.Indian/N. Alask.	0	0.0%
N. Hawaiian/P. Isl.	0	0.0%
Asian	0	0.0%
Other	5	6.8%
<b>Ethnicity</b>		
Hispanic/Latino	21	28.4%
Not Hispanic/Latino	53	71.6%
<b>Fitzpatrick Skin Phototype</b>		
I	4	5.4%
II	21	28.4%
III	19	25.7%
IV	20	27.0%
V	7	9.5%
VI	3	4.1%

<sup>a</sup> Number of subjects in the ITT populations

### 4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total median volume of RHA<sup>®</sup> 3 injected to achieve optimal correction results was 1.4 mL. The proportion of subjects who received touch-up treatment with RHA<sup>®</sup> 3 at Week 2 was 67.6%.

In general, a linear threading or fan-like technique, or combination, was used for 90.3% of the subjects treated with RHA<sup>®</sup> 3.

### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA<sup>®</sup> 3. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA<sup>®</sup> 3 compared to the improvement from pre-injection of the NLF treated with the control treatment, as assessed (using the WSRS) by the BLE at 24 weeks after baseline; results are presented in Table 4.

**Table 4. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study**

	n <sup>a</sup>	RHA <sup>®</sup> 3		Control Device	
		WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>	WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>
Pre-treatment <sup>d</sup>	62	3.39	-	3.39	-
Week 24	62	2.06	1.32	2.16	1.23
Week 36	58	2.36	1.03	2.41	0.98
Week 52	56	2.45	0.91	2.54	0.82
Week 64	47	2.47	0.91	2.55	0.83

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits

<sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

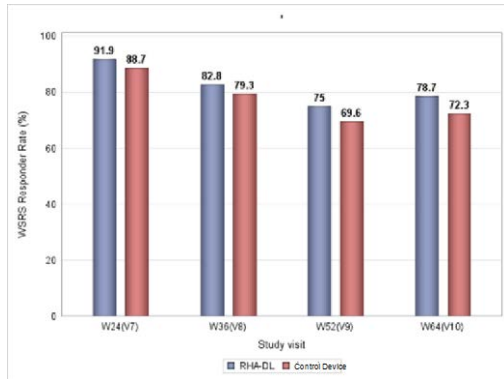
<sup>c</sup> Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

<sup>d</sup> Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA<sup>®</sup> 3 at 24 weeks for the treatment of NLFs. Results also showed that RHA<sup>®</sup> 3 was not inferior to the control treatment at all study visits.

Throughout the follow-up period, the aesthetic improvement of the RHA<sup>®</sup> 3 treated NLF continued to be clinically significant ( $\geq 1$  grade difference from pre-treatment on the WSRS) for more than 78% of the subjects at 64 weeks after initial treatment (Figure 1).

**Figure 1. Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA<sup>®</sup> 3 and the Control Device**



	Week 24	Week 36	Week 52	Week 64
RHA <sup>®</sup> 3	91.9%	82.8%	75.0%	78.7%
Control Device	88.7%	79.3%	69.6%	72.3%

PP populations at the respective follow-up visits

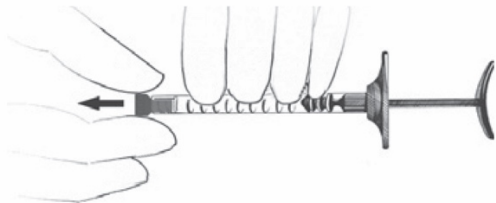
Rate of responders:  $\geq 1$  grade difference from pre-treatment on the WSRS

On the Global Aesthetic Improvement (GAI) scale, more than 81% of the subjects and the BLE reported that the NLF treated with RHA<sup>®</sup> 3 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q<sup>®</sup> questionnaire with the mean score improving from 29 to more than 63 throughout the follow-up period. More than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained at more than 82% at 64 weeks.

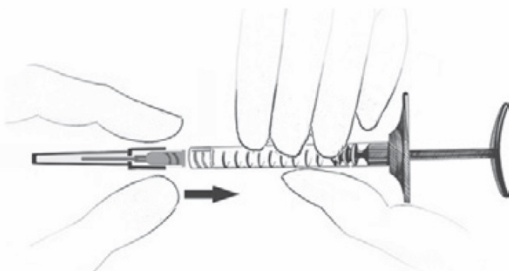
More than 77% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

**DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE**

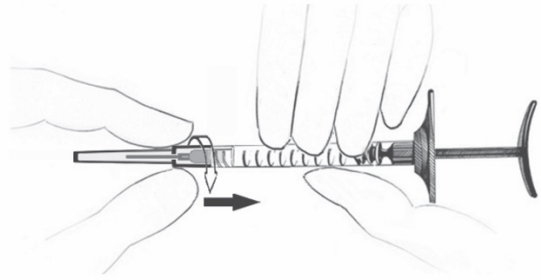
1. Remove the stopper from the syringe by pulling it off.



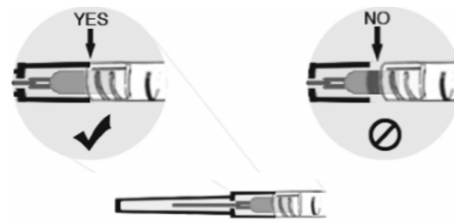
2. Insert the screw thread of the needle firmly into the syringe end-piece.



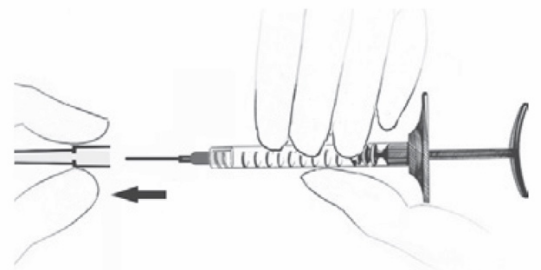
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



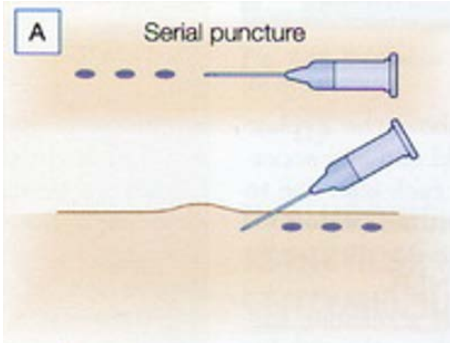
**PRE-TREATMENT GUIDELINES**

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) 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 with RHA<sup>®</sup> 3 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.
- Sterile gloves are recommended while injecting RHA<sup>®</sup> 3.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

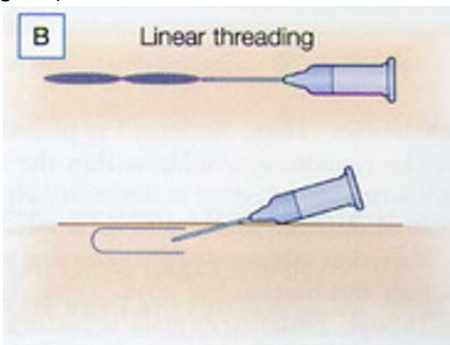
## INJECTION TECHNIQUES

- RHA<sup>®</sup> 3 is administered by using a thin gauge needle (27 G x ½"). The needle is inserted into the mid-to-deep dermis at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA<sup>®</sup> 3 can be injected by a number of different techniques that depend on the injector's experience and preference, and patient characteristics.

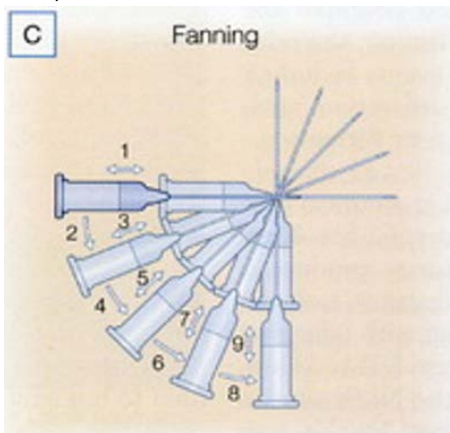
**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



**B. Linear threading:** the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a "thread", while withdrawing (retrograde) or pushing (antegrade) the needle.



**C. Fanning technique:** the needle is introduced as for the *Linear threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA<sup>®</sup> 3 is injected slowly into the mid-to-deep dermis. If the injection is made too deeply, i.e. into sub-cutaneous tissue, the correction may not be as expected. It is possible to tell when an injection is being made too deeply because subcutaneous tissue

does not offer any resistance to product injection, unlike the dermis.

- If the color of the needle 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 pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0mL per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles need further treatment with RHA<sup>®</sup> 3, the same procedure should be repeated until a satisfactory result is obtained.

## POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- 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.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

## STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Obtain prompt medical attention if injury with used needle occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA<sup>®</sup> 3 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA<sup>®</sup> 3 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

## PATIENT INSTRUCTIONS

Patient information brochure is available on request, or via the website [www.teoxane-us-distributor.com](http://www.teoxane-us-distributor.com).

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

- Patients should be advised not to wear make-up during 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 Teoxane US Distributor at (000) 000-0000.



Catalogue number



Lot / batch number



Expiration date (YYYY-MM-DD)



Consult Instructions for use



Single use only



Sterilized using steam



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

### HOW SUPPLIED

RHA<sup>®</sup> 3 is supplied in individual blisters containing a 1mL treatment syringe with two 27 G x ½” needles as indicated on the carton.

The content of the syringe is sterile and non-pyrogenic. Do not resterilize. 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<sup>®</sup> 3 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.

**RxOnly**

#### **Manufactured by:**

TEOXANE SA.  
Rue de Lyon, 105  
1203 Geneva  
Switzerland

#### **Distributed by:**

Teoxane US Distributor  
Address  
City, State, Zip Code  
U.S.A.

RHA<sup>®</sup> is a registered trademark of TEOXANE SA.

### SYMBOLS



Manufacturer's name and address

## RHA<sup>®</sup> 4

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

**BEFORE USING RHA<sup>®</sup> 4, PLEASE READ THE FOLLOWING INFORMATION THOROUGHLY**

### DEVICE DESCRIPTION

RHA<sup>®</sup> 4 is a viscoelastic, sterile, non-pyrogenic, clear, colorless, homogeneous and biodegradable gel implant. It is produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 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<sup>®</sup> 4 also contains 0.3% lidocaine hydrochloride to reduce pain on injection.

### INTENDED USE / INDICATIONS

RHA<sup>®</sup> 4 is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

### CONTRAINDICATIONS

- RHA<sup>®</sup> 4 is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- RHA<sup>®</sup> 4 contains trace amounts of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- RHA<sup>®</sup> 4 should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA<sup>®</sup> 4 should not be used in patients with bleeding disorders.

### WARNINGS

- RHA<sup>®</sup> 4 must not be injected into blood vessels. Introduction of product into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment or blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms: changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- Product use at 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 for details.

- Inflammatory reaction, anaphylactic reaction, papule, acne, blisters, scarring, papules, unsatisfactory, results, scarring 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.
- 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<sup>®</sup> 4 should be used with caution in patients on immunosuppressive therapy.
- Bruising or bleeding may occur at RHA<sup>®</sup> 4 injection sites. RHA<sup>®</sup> 4 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<sup>®</sup> 4 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<sup>®</sup> 4, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RHA<sup>®</sup> 4 is administered before the skin has healed completely after such a procedure.
- RHA<sup>®</sup> 4 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<sup>®</sup> 4 is packaged for single-patient use. Do not reuse a syringe between two treatments and/or between two patients. Do not resterilize.
- 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. Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the Luer-lock and needle hub connection.
- RHA<sup>®</sup> 4 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 TEOXANE US Distributor at (000) 000-0000.

## ADVERSE EXPERIENCES

### 1. Clinical Evaluation of RHA<sup>®</sup> 4

A multicenter, controlled, randomized, double-blinded, within-subject (split-face), prospective US clinical study compared the safety of RHA<sup>®</sup> 4 versus a control treatment for the treatment of moderate to severe nasolabial folds, and demonstrated similar safety profiles. 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 14-day diary after each injection.

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

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

- The most frequent CTRs were swelling, firmness, tenderness, redness, lumps/bumps, pain, and bruising.
- Proportions of subjects experiencing at least one CTR of each category was similar between RHA<sup>®</sup> 4 and Control treatment.
- More than 67% of the CTRs had resolved by Day 7.
- The majority (80%) of CTRs had resolved by Day 14.
- There were almost 3 times less subjects who reported severe CTR with RHA<sup>®</sup> 4 than with Control treatment.
- For nearly all CTRs (more than 90%) experienced by any treatment group (initial treatment or touch-up treatment), the maximal severity reported was "Mild" or "Moderate".

**Table 1. Common Treatment Responses by maximum severity after initial treatment with RHA<sup>®</sup> 4 and the Control Device – Safety Population**

Common Treatment Responses	TOTALS		RHA <sup>®</sup> 4 (N <sup>a</sup> =120 NLF)			Control Device (N <sup>a</sup> =120 NLF)		
	RHA <sup>®</sup> 4 n <sup>b</sup> %	CTRL <sup>c</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %	Mild n <sup>b</sup> %	Mod <sup>d</sup> n <sup>b</sup> %	Sev <sup>e</sup> n <sup>b</sup> %
Bruising	70 58.3%	72 60.0%	35 29.2%	26 21.7%	9 7.5%	37 30.8%	25 20.8%	10 8.3%
Discoloration	50 41.7%	56 46.7%	30 25.0%	16 13.3%	4 3.3%	30 25.0%	20 16.7%	6 5.0%
Firmness	91 75.8%	93 77.5%	36 30.0%	46 38.3%	9 7.5%	13 10.8%	50 41.7%	30 25.0%
Itching	30 25.0%	44 36.7%	25 20.8%	5 4.2%	0 0.0%	28 23.3%	14 11.7%	2 1.7%
Lumps/Bumps	81 67.5%	90 75.0%	36 30.0%	33 27.5%	12 10.0%	28 23.3%	37 30.8%	25 20.8%
Pain	66 55.0%	87 72.5%	42 35.0%	19 15.8%	5 4.2%	30 25.0%	40 33.3%	17 14.2%
Redness	84 70.0%	91 75.8%	42 35.0%	38 31.7%	4 3.3%	32 26.7%	42 35.0%	17 14.2%
Swelling	97 80.8%	104 86.7%	41 34.2%	44 36.7%	12 10.0%	21 17.5%	38 31.7%	45 37.5%
Tenderness	90 75.0%	95 79.2%	53 44.2%	30 25.0%	7 5.8%	23 19.2%	45 37.5%	27 22.5%

<sup>a</sup> Number of subjects' NLF treated with the respective device

<sup>b</sup> Number of subjects' NLF with any specific Common Treatment Response

<sup>c</sup> CTRL = Control treatment

<sup>d</sup> Mod = Moderate

<sup>e</sup> Sev = Severe

**Table 2. Duration of Common Treatment Responses after initial treatment with RHA<sup>®</sup> 4 and the Control Device – Safety Population**

Common Treatment Responses	RHA <sup>®</sup> 4 (N <sup>a</sup> =120 NLF) N <sup>b</sup> %				Control Device (N <sup>a</sup> =120 NLF) N <sup>b</sup> %			
	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>	1-3 Days	4-7 Days	8-14 Days	Last Day <sup>d</sup>
Bruising	22 18.3%	28 23.3%	20 16.7%	8 6.7%	37 30.8%	28 23.3%	7 5.8%	4 3.3%
Discoloration	28 23.3%	10 8.3%	12 10.0%	10 8.3%	34 28.3%	14 11.7%	8 6.7%	4 3.3%
Firmness	16 13.3%	20 16.7%	55 45.8%	35 29.2%	13 10.8%	26 21.7%	54 45.0%	26 21.7%
Itching	20 16.7%	8 6.7%	2 1.7%	2 1.7%	24 20.0%	14 11.7%	6 5.0%	3 2.5%
Lumps/Bumps	19 15.8%	14 11.7%	48 40.0%	36 30.0%	25 20.8%	24 20.0%	41 34.2%	27 22.5%
Pain	48 40.0%	12 10.0%	6 5.0%	3 2.5%	54 45.0%	25 20.8%	8 6.7%	2 1.7%
Redness	42 35.0%	30 25.0%	12 10.0%	8 6.7%	42 35.0%	37 30.8%	12 10.0%	7 5.8%
Swelling	36 30.0%	29 24.2%	32 26.7%	16 13.3%	27 22.5%	51 41.7%	27 22.5%	11 9.2%
Tenderness	41 34.2%	22 18.3%	27 22.5%	14 11.7%	26 21.7%	39 32.5%	30 25.0%	8 6.7%

<sup>a</sup> Number of subject NLF treated with the respective device

<sup>b</sup> Number of subject NLF with each specific CTR by maximum duration

<sup>c</sup> Duration refers to number of days cited in the patient diary, irrespective of date of injection

<sup>d</sup> The CTR numbers indicated in the "Last Day" column are also included in the "8-14 Days" column.

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.

- All treatment-related AEs were mild or moderate in severity.
- The vast majority of treatment-related AEs experienced by both treatment groups were typical of the expected signs and symptoms observed following an injection of a dermal filler.
- All treatment-related AEs were temporally associated with a recent device (RHA<sup>®</sup> 4 or control treatment) injection.
- Nearly all treatment-related AEs were based on subjects' diary entries (CTRs). Also, there were 11 treatment-related AEs (all of mild severity) in 11 subjects with RHA<sup>®</sup> 4 reported by the Treating Investigator which consisted of acne, discoloration, firmness, headache, pain, swelling, telangiectasia, and tenderness.
- No events were deemed to be a granuloma.
- There were no late onset treatment-related AEs.
- There were no treatment-related serious AEs.

### 2. Post-marketing Surveillance

The following adverse events were reported as part of post-marketing surveillance on the use of RHA<sup>®</sup> 4 outside the US. These adverse events are listed in order of prevalence: swelling, lumps and bumps, firmness, edema, implant migration and unsatisfactory result.

In some cases the symptoms resolved without any treatment. Reported treatments included the use of (in alphabetical order): antibiotics, hyaluronidase and steroids. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

## CLINICAL STUDY

The safety and effectiveness of RHA<sup>®</sup> 4 in the correction of moderate to severe facial wrinkles and folds was evaluated in a US pivotal clinical study described hereafter.

### 1. Pivotal Study Design

A controlled, randomized, double-blinded, within-subject, multicenter, prospective pivotal clinical study was conducted to evaluate the clinical safety and effectiveness of RHA<sup>®</sup> 4.

Subjects were randomly assigned to receive RHA<sup>®</sup> 4 and a control treatment in deep dermis to superficial subcutaneous for the treatment of moderate to severe nasolabial folds, or to a non-treatment group. The side of the face for each device injected was assigned randomly. If deemed necessary by the Treating Investigator, additional NLF correction was performed after 2 weeks (touch-up), with the same study device used for initial treatment.

The follow-up period consisted of safety and effectiveness follow-up visits at 4, 12, 24, 36, 52, and 64 weeks after the last treatment. Subjects were eligible for optional retreatment if necessary at Weeks 24 or 36. Subjects were also offered retreatment at Week 52 or Week 64, and were then followed for 1 month after retreatment or until all Adverse Events (AEs) resolve. Retreatment on either side was provided using RHA<sup>®</sup> 4 (the Control treatment was not used).

Subjects randomized to the “no treatment” control group did not receive treatment.

### 2. Study Endpoints

The primary effectiveness endpoint was the analysis of non-inferiority of RHA<sup>®</sup> 4 versus the Control treatment, in terms of change from pre-injection to 24 weeks after injection, as measured by the Blinded Live Investigator (BLE) using a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as Wrinkle Severity Rating Scale (WSRS) score.

Secondary effectiveness endpoints included rates of responders ( $\geq 1$  grade difference from pre-treatment on the WSRS), as measured by the BLE (see data in Figure 1), Global Aesthetic Improvement (GAI), as assessed by the subject and by the BLE, impact and effectiveness of study treatment procedures from the subjects’ perspective as assessed by the nasolabial fold domain of the FACE-Q<sup>®</sup>, and subject satisfaction. Safety endpoints was evaluated throughout the study, with a 14-day subject diary capturing post-injection signs/symptoms following every study injection, and AE assessments at each visit, and included self-assessment of injection site pain by the subject using a Visual Analog Scale.

### 3. Demographics

A total of 120 subjects (27 to 86 years old) were allocated to RHA<sup>®</sup> 4 and Control treatment, and 20 were allocated to untreated controls. 118 subjects were included in the ITT population.

Subject’s demographics are presented in Table 3.

**Table 3. Demographics**

Number / % of subjects	RHA <sup>®</sup> 4 versus Control Device N <sup>†</sup> =118	
<b>Age</b>		
Mean (SD)	57.4	(10.0)
min max	27	86
<b>Gender</b>		
Female	106	89.8%
Male	12	10.2%
<b>Race</b>		
Caucasian	97	82.2%
Black	19	16.1%
Am.Indian/N. Alask.	1	0.9%
N. Hawaiian/P. Isl.	0	0.0%
Asian	1	0.9%
Other	0	0.0%
<b>Ethnicity</b>		
Hispanic/Latino	30	25.4%
Not Hispanic/Latino	88	74.6%
<b>Fitzpatrick Skin Phototype</b>		
I	4	3.4%
II	21	17.8%
III	40	33.9%
IV	31	26.3%
V	14	11.9%
VI	8	6.8%

<sup>†</sup> Number of subjects in the ITT populations

### 4. Treatment Characteristics

The study protocol allowed a maximum of 3.0 mL in a single NLF per treatment session. The overall total median volume of RHA<sup>®</sup> 4 injected to achieve optimal correction results was 1.7 mL. The proportion of subjects who received touch-up treatment with RHA<sup>®</sup> 4 at Week 2 was 27.1%.

In general, a linear threading or multiple punctate pools technique, or combination, was used for 84.2% of the subjects treated with RHA<sup>®</sup> 4.

### 5. Effectiveness Results

The primary effectiveness endpoint was met for RHA<sup>®</sup> 4. The primary effectiveness endpoint was the aesthetic improvement from pre-injection of the NLF treated with RHA<sup>®</sup> 4 compared to the improvement from pre-injection of the NLF treated with the Control treatment, as assessed (using the WSRS) by the BLE at 24 weeks after baseline, and results are presented in Table 4.

**Table 4. Wrinkle Severity Rating Scale scores assessed by a Blinded Live Evaluator throughout the study**

	n <sup>a</sup>	RHA <sup>®</sup> 4		Control Device	
		WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>	WSRS score <sup>b</sup>	WSRS Improvement <sup>c</sup>
Pre-treatment	88	3.49	-	3.49	-
Week 24 <sup>d</sup>	88	2.15	1.34	2.33	1.16
Week 36	86	2.21	1.28	2.37	1.12
Week 52	77	2.25	1.23	2.43	1.05
Week 64	65	2.20	1.26	2.35	1.11

<sup>a</sup> Number of subjects in the PP populations at the respective follow-up visits

<sup>b</sup> Mean Wrinkle Severity Rating Scale score (higher scores mean deepest wrinkles)

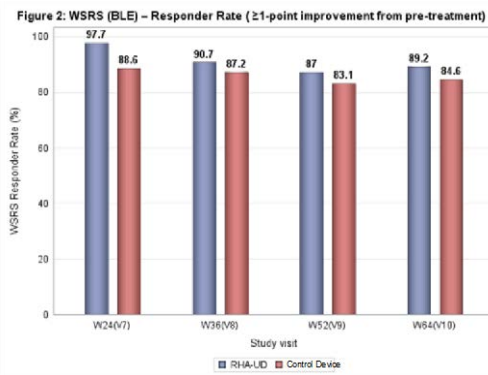
<sup>c</sup> Mean Wrinkle Severity Rating Scale improvement from pre-treatment (higher scores mean more improvement from pre-treatment)

<sup>d</sup> Primary effectiveness endpoint

The results demonstrated that non-inferiority to the control was achieved for RHA<sup>®</sup> 4, at 24 weeks for the treatment of NLFs. Results also showed that RHA<sup>®</sup> 4 was not inferior to the Control treatment at all study visits.

Throughout the follow-up period, the aesthetic improvement of the RHA<sup>®</sup> 4 treated NLF continued to be clinically significant ( $\geq 1$  grade difference from pre-treatment on the WSRS) for more than 89% of the subjects at 64 weeks after initial treatment (Figure 1).

**Figure 1. Proportion of responders on the Wrinkle Severity Rating Scale measured by a Blinded Live Evaluator for RHA<sup>®</sup> 4 and the Control Device**



	Week 24	Week 36	Week 52	Week 64
RHA <sup>®</sup> 4	97.7%	90.7%	87.0%	89.2%
Control Device	88.6%	87.2%	83.1%	84.6%

PP populations at the respective follow-up visits

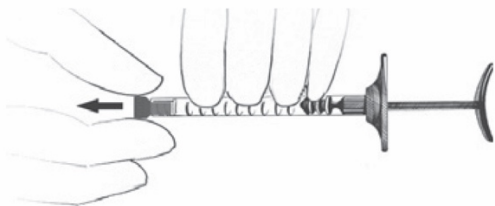
Rate of responders:  $\geq 1$  grade difference from pre-treatment on the WSRS

On the Global Aesthetic Improvement (GAI) scale, more than 87% of the subjects and the BLE reported that the NLF treated with RHA<sup>®</sup> 4 was improved or very much improved from week 24 to week 64. The subjects consistently reported improvement up to 64 weeks based on the NLF module of the FACE-Q<sup>®</sup> questionnaire with the mean score improving from 24 to more than 70 throughout the follow-up period. More than 93% of the subjects reported to be satisfied or very satisfied from week 24 to week 64.

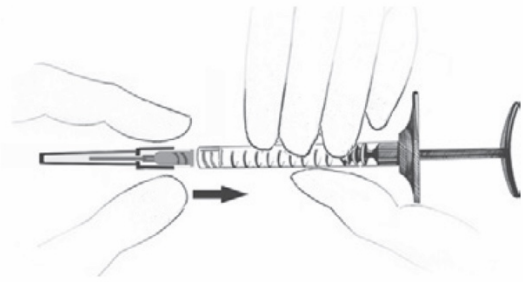
More than 75% of the subjects received repeat treatment. The effectiveness and safety profiles after repeat treatment were similar to that after initial treatment.

**DIRECTIONS FOR ASSEMBLY OF THE NEEDLE TO THE SYRINGE**

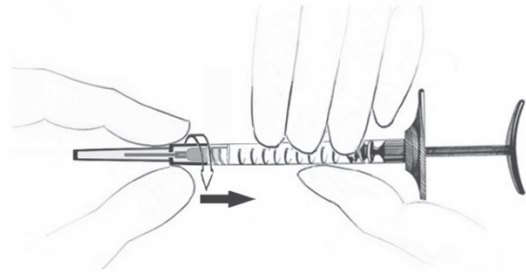
1. Remove the stopper from the syringe by pulling it off.



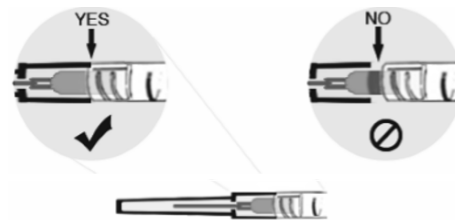
2. Insert the screw thread of the needle firmly into the syringe end-piece.



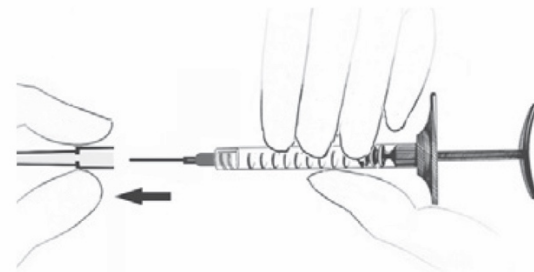
3. Screw the needle clockwise, while maintaining slight pressure between the needle and the syringe.



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



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



**PRE-TREATMENT GUIDELINES**

- Prior to treatment, the patient should avoid taking medications or supplements which thin the blood (e.g., aspirin, nonsteroidal anti-inflammatory medications, St. John's Wort, or high doses of Vitamin E supplements) 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 with RHA<sup>®</sup> 4 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



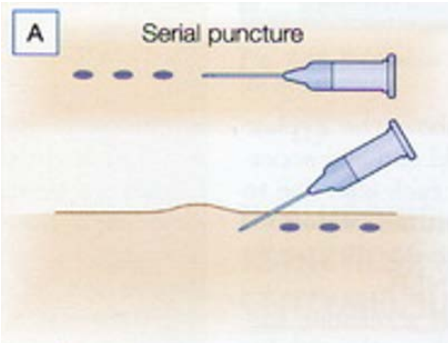
be washed with soap and water and dried with a clean towel. Cleanse the area to be treated with alcohol or another suitable antiseptic solution.

- Sterile gloves are recommended while injecting RHA<sup>®</sup> 4.
- Before injecting, prime the needle by carefully pressing the syringe plunger until a small droplet of the gel is visible at the tip of the needle.

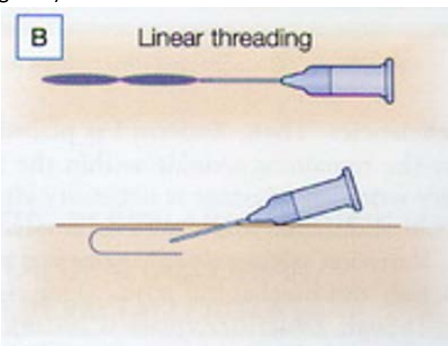
### INJECTION TECHNIQUES

- RHA<sup>®</sup> 4 is administered by using a thin gauge needle (27 G x ½”). The needle is inserted into the deep dermis to superficial subcutaneous at an approximate angle of 15° to 30° parallel to the length of the wrinkle or fold.
- RHA<sup>®</sup> 4 can be injected by a number of different techniques that depend on the injector’s experience and preference, and patient characteristics.

**A. Serial puncture:** consists of multiple injections, evenly and closely spaced all along wrinkles or folds. This technique is considered to be more precise, but may result in more discomfort for the patient due to the number of punctures.



**B. Linear threading:** the needle is fully introduced in the wrinkle or the fold, and the product is injected along the line, as a “thread”, while withdrawing (retrograde) or pushing (antegrade) the needle.



**C. Fanning technique:** the needle is introduced as for the *Linear threading technique*, and the product is injected along several closely spaced lines, by changing the direction of the needle, all using the same puncture site (the needle is not withdrawn).



- RHA<sup>®</sup> 4 is injected slowly into the deep dermis to superficial subcutaneous.
- If the color of the needle 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 pulling the syringe out of the skin, to prevent product from leaking out, or product misplacement (too superficially in the skin).
- The volume to be injected depends on the corrections to be performed, but it is important to not overcorrect. Based on the US clinical study, patients should be limited to 6.0mL per patient per treatment session in wrinkles and folds such as NLFs. The safety of injecting greater amounts has not been established.
- If blanching is observed (e.g., the overlying skin turns a whitish color), the injection should be stopped immediately and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
- If the wrinkles need further treatment with RHA<sup>®</sup> 4, the same procedure should be repeated until a satisfactory result is obtained.

### POST-TREATMENT GUIDELINES

- When the injection is completed, the treated site should be gently massaged so that it conforms to the contour of the surrounding tissues. If an overcorrection has occurred, massage the area firmly between your fingers or against an underlying area to obtain optimal results.
- 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.
- After use, syringes may be potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical biohazard devices. Obtain prompt medical attention if injury occurs.

### STERILE NEEDLES

- After use, needles are potential biohazards. Follow national, local, or institutional guidelines for use and disposal of medical sharp devices (e.g. discard uncapped needles in approved sharps containers).
- Obtain prompt medical attention if injury with used needle occurs.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.

- Do not recap needles. Recapping by hand is a hazardous practice and should be avoided.
- RHA<sup>®</sup> 4 is provided with 2 needles that do not contain engineered injury protection. Administration of RHA<sup>®</sup> 4 requires direct visualization and complete and gradual insertion of the needle making engineered protection devices not feasible. Care should be taken to avoid sharps exposure by proper environmental controls.

### **PATIENT INSTRUCTIONS**

Patient information brochure is available on request, or via the website [www.teoxane-us-distributor.com](http://www.teoxane-us-distributor.com).

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

- Patients should be advised not to wear make-up during 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 Teoxane US Distributor at (000) 000-0000.

### **HOW SUPPLIED**

RHA<sup>®</sup> 4 is supplied in individual blisters containing a 1mL treatment syringe with two 27 G x ½" needles as indicated on the carton.

The content of the syringe is sterile and non-pyrogenic. Do not resterilize. 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<sup>®</sup> 4 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.

### **Manufactured by:**

TEOXANE SA.  
Rue de Lyon, 105  
1203 Geneva  
Switzerland

### **Distributed by:**

Teoxane US Distributor  
Address  
City, State, Zip Code  
U.S.A.

RHA<sup>®</sup> is a registered trademark of TEOXANE SA.

### **SYMBOLS**



Manufacturer's name and address



Catalogue number



Lot / batch number



Expiration date (YYYY-MM-DD)



Consult Instructions for use



Single use only



Sterilized using steam



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

**RxOnly**