

# **EVOLENCE<sup>®</sup>**

## **Collagen Filler**

### Instructions for Use

8 June 09

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

#### **DEVICE DESCRIPTION**

**EVOLENCE<sup>®</sup>** Collagen Filler is a porcine collagen gel implant composed of 3.5% (35 mg/ml) homogenous Type I collagen that was extracted and purified from porcine tendons and suspended in phosphate-buffered saline (PBS) and which has been cross linked with a ribose mediated (GLYMATRIX<sup>™</sup>) technology. **EVOLENCE<sup>®</sup>** is supplied as single use pre-filled sterile syringe.

#### **INDICATIONS FOR USE**

**EVOLENCE<sup>®</sup>** Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

#### **CONTRAINDICATIONS**

**EVOLENCE<sup>®</sup>** Collagen Filler is contraindicated in the following:

- Patients with known hypersensitivity to any collagen products or planning to undergo desensitization injections to porcine products, as these injections can contain porcine collagen.
- Patients with a history of anaphylactic reactions or history or presence of severe recurrent allergic reactions.
- **EVOLENCE<sup>®</sup>** Collagen Filler should not be implanted in spaces other than the dermis of the face.
- **EVOLENCE<sup>®</sup>** Collagen Filler should not be implanted in patients with bleeding disorders.

#### **WARNINGS**

- Local necrosis is a rare event, which has been observed following other collagen implantation and may occur following injections to the glabella. It is thought to result from the injury, obstruction, or compromise of blood vessels.
- Patients with a history of dietary porcine allergy should be carefully examined before porcine collagen injections, since it is possible that the collagen component of the porcine material may be causing the allergy.
- Avoid injecting **EVOLENCE<sup>®</sup>** into blood vessels as collagen can initiate platelet aggregation and may cause vascular occlusion and localized infarction or embolic phenomena.

- Use of **EVOLENCE**<sup>®</sup> at specific sites in which infections or active inflammatory reaction is present, should be deferred until the underlined process has been controlled.
- Injection site reactions (e.g., swelling, redness, tenderness, or pain) to **EVOLENCE**<sup>®</sup> have been observed as consisting mainly of short-term minor or moderate inflammatory symptoms starting early after treatment and with less than 7 days duration. Refer to the adverse reactions section for details.
- Delayed onset inflammatory papules have been reported following the use of dermal fillers. Inflammatory papules (solid, raised skin lesions less than 1 cm in diameter) that may occur rarely should be considered and treated as a soft tissue infection.

## PRECAUTIONS

The following precautions must be observed:

- **STERILE CONTENT.** The prefilled syringe is intended for single patient use. Do not resterilize. Do not use if the package is opened or damaged.
- As with all transcutaneous procedures, injection of **EVOLENCE**<sup>®</sup> carries a risk of infection. The usual precautions associated with injectable material should be followed.
- Bruising or bleeding may occur at **EVOLENCE**<sup>®</sup> injection sites. Patients using substances, which may reduce coagulation, such as aspirin and non-steroidal anti-inflammatory drugs, may experience increased bruising or bleeding at injection sites as experienced with any injection.
- The safety and effectiveness of **EVOLENCE**<sup>®</sup> for the treatment of anatomic regions other than facial wrinkles and nasolabial folds has not been established in controlled clinical studies.
- The safety and efficacy of **EVOLENCE**<sup>®</sup> for lip augmentation has not been established.
- The safety of usage in breast augmentation or injection into bone, tendon, ligament or muscle has not been established in controlled clinical studies.
- **EVOLENCE**<sup>®</sup> should be used with caution in patients on immunosuppressive therapy.
- The safety of **EVOLENCE**<sup>®</sup> in pregnant or breastfeeding females, as well as in patients under 18 years of age has not been established.
- The safety of **EVOLENCE**<sup>®</sup> with concomitant dermal therapies such as epilation, UV radiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials, therefore there are no data available on the potential for site inflammatory reaction.
- Injection of **EVOLENCE**<sup>®</sup> into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- Patients should minimize exposure of the treated areas to excessive sun, UV lamp exposure and extreme hot or cold weather for the first 24-48 hours following treatment.
- Based on preclinical studies the use of **EVOLENCE**<sup>®</sup> in individual patients shall be limited to 10 ml over a one year period. The safety of injecting greater amounts has not been established. In clinical trials using a split face design,

patients were injected with up to approximately 4 mL of **EVOLENCE**<sup>®</sup> in a single injection site over a one year time period.

- The safety of **EVOLENCE**<sup>®</sup> in patients susceptible to keloid formation, hyperpigmentation and hypertrophic scarring has not been established.
- Long term safety and effectiveness of **EVOLENCE**<sup>®</sup> beyond one year have not been investigated in clinical trials.
- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state, and federal requirements.
- **EVOLENCE**<sup>®</sup> should not be mixed with other products before implantation of the device.
- **EVOLENCE**<sup>®</sup> is a yellowish, homogenous, opaque gel. In the event that a syringe contains material exhibiting separation between solid and liquid, or change of color, do not use the syringe and notify OrthoDermatologics at 1-800-386-5362.

## **ADVERSE EVENTS**

### **Clinical Evaluation of **EVOLENCE**<sup>®</sup> Collagen Filler**

A randomized, comparative trial to evaluate the safety and efficacy of **EVOLENCE**<sup>®</sup> was conducted at 6 clinical centers. One hundred and forty nine (149) subjects were injected with **EVOLENCE**<sup>®</sup> into one nasolabial fold (NLF) and the Hyaluronic Acid-based dermal filler (HA Control Product) into the contralateral NLF.

Each subject recorded treatment symptoms up to 14 days following initial injection and up to resolution of any event following the touch up facial injection in the subject's diary. Subjects were instructed to rate each common treatment response listed in the diary as Mild, Moderate, Severe or None. Each subject also was evaluated for adverse events by the study investigators at each of multiple follow-up visits through 12 months.

Injection site responses (symptom related AE) reported by >5% of subjects or observed by the study investigators in either treatment group are summarized in tables 1 and 2. All observed adverse events are included; No adverse events other than those listed in Table 1 and 2 were observed by any study subject or investigator.

**Table 1: Number & (%) of Subjects with AEs at the Injection Site\* by Maximum Severity – for Adverse Events Occurring in >5% of Subjects, as Reported in Subjects' Diaries and Physician Case Report Forms**

	EVOLENCE <sup>®</sup> (Total N = 149)				HA Control Product ( Total N = 149)			
	Overall Incidence	Mild	Mod	Severe	Overall Incidence	Mild	Mod	Severe
<b>Injection Site Conditions<sup>†</sup></b>	123 (82.6)	111 (74.5)	11 (7.4)	1 (0.7)	130 (87.2)	113 (75.8)	16 (10.7)	1 (0.7)
Pain	84 (56.4)	77 (51.7)	6 (4.0)	1 (0.7)	95 (63.8)	85 (57.0)	10 (6.7)	0
Erythema	86 (57.8)	83 (55.7)	2 (1.3)	1 (0.7)	89 (59.7)	84 (56.4)	5 (3.4)	0
Swelling	80 (53.7)	74 (49.7)	5 (3.4)	1 (0.7)	102 (68.5)	94 (63.1)	8 (5.4)	0
Bruising	54 (36.2)	52 (34.9)	2 (1.3)	0	71 (47.7)	63 (42.3)	7 (4.7)	1 (0.7)
Pruritus	23 (15.4)	23 (15.4)	0	0	25 (16.8)	25 (16.8)	0	0
Induration	20 (13.4)	17 (11.4)	3 (2.0)	0	9 (6.0)	8 (5.4)	1 (0.7)	0

Mod = Moderate

\* Adverse events occurring after the first facial injection.

As detailed in Table 1, 123 of the 149 subjects who were treated with **EVOLENCE<sup>®</sup>** and 130 of the 149 subjects who were treated with the HA Control product reported injection site reactions. Of those reported, in the **EVOLENCE<sup>®</sup>** group 326 reactions were reported as mild, 18 as moderate and 3 severe. In the HA Control group, 359 reactions were reported as mild, 31 as moderate and 1 severe.

The following disorders at the injection site were reported as either **EVOLENCE<sup>®</sup>**-related or HA Control Product-related in at least 5% of the subjects: pain, erythema, swelling, bruising, pruritus, and induration. Adverse events in this category that occurred more commonly ( $\geq 5\%$  difference) for HA Control Product vs. **EVOLENCE<sup>®</sup>** treated patients respectively, were site pain (63.8% vs. 56.4%), swelling (68.5% vs. 53.7%) and bruising (47.7% vs. 36.2%) The only AE to occur more commonly in the **EVOLENCE<sup>®</sup>** treated group ( $\geq 5\%$  difference) was induration (13.4% vs. 6.0%).

No other AEs were reported to be related to either **EVOLENCE<sup>®</sup>** or HA Control Product in more than 2 subjects (1.3%). Serious AEs reported in 2 subjects were Atrial septal defect and Metastatic colon cancer to ovaries.

**Table 2: Number (%) of Subjects with Skin Reactions (Occurring in >5% of Subjects) to Study Product by Injection and Maximum Duration, as Reported in Subjects' Diaries and Physician Case Report Forms**

	After First Facial Injection*							
	EVOLENCE® (N = 149)				HA Control Product (N = 149)			
	≤ 3	4-7	8-14	>14	≤ 3	4-7	8-14	>14
No. of Subjects†	<u>96</u> (64.4)	<u>66</u> (44.3)	<u>17</u> (11.4)	<u>17</u> (11.4)	<u>99</u> (66.4)	<u>70</u> (47.0)	<u>28</u> (18.8)	<u>13</u> (8.7)
No. of Episodes	<u>200</u>	<u>94</u>	<u>25</u>	<u>21</u>	<u>209</u>	<u>124</u>	<u>34</u>	<u>21</u>
Erythema‡	<u>52</u> (34.9)	<u>21</u> (14.1)	<u>4</u> (2.7)	<u>3</u> (2.0)	<u>48</u> (32.2)	<u>27</u> (18.1)	<u>4</u> (2.7)	<u>4</u> (2.7)
Swelling‡	<u>43</u> (28.9)	<u>21</u> (14.1)	<u>8</u> (5.4)	<u>2</u> (1.3)	<u>54</u> (36.2)	<u>31</u> (20.8)	<u>5</u> (3.4)	<u>7</u> (4.7)
Induration‡	<u>6</u> (4.0)	<u>2</u> (1.3)	<u>1</u> (0.7)	<u>7</u> (4.7)	<u>2</u> (1.3)	<u>3</u> (2.0)	<u>1</u> (0.7)	<u>2</u> (1.3)
Bruising‡	<u>19</u> (12.8)	<u>22</u> (14.8)	<u>7</u> (4.7)	<u>1</u> (0.7)	<u>16</u> (10.7)	<u>31</u> (20.8)	<u>16</u> (10.7)	<u>4</u> (2.7)
Pain‡	<u>48</u> (32.2)	<u>24</u> (16.1)	<u>5</u> (3.4)	<u>5</u> (3.4)	<u>57</u> (38.3)	<u>27</u> (18.1)	<u>7</u> (4.7)	<u>3</u> (2.0)
Pruritus‡	<u>17</u> (11.4)	<u>2</u> (1.3)	<u>0</u>	<u>1</u> (0.7)	<u>17</u> (11.4)	<u>3</u> (2.0)	<u>1</u> (0.7)	<u>0</u>
	After Second Facial Injection§							
	EVOLENCE® (N = 74)				HA Control Product (N = 74)			
	≤ 3	4-7	8-14	>14	≤ 3	4-7	8-14	>14
No. of Subjects†	<u>32</u> (43.2)	<u>12</u> (16.2)	<u>4</u> (5.4)	<u>6</u> (8.1)	<u>35</u> (47.3)	<u>20</u> (27.0)	<u>3</u> (4.1)	<u>4</u> (5.4)
No. of Episodes	<u>57</u>	<u>21</u>	<u>6</u>	<u>9</u>	<u>65</u>	<u>29</u>	<u>4</u>	<u>5</u>
Erythema‡	<u>14</u> (18.9)	<u>4</u> (5.4)	<u>3</u> (4.1)	<u>4</u> (5.4)	<u>12</u> (16.2)	<u>9</u> (12.2)	<u>1</u> (1.4)	<u>3</u> (4.1)
Swelling‡	<u>13</u> (17.6)	<u>8</u> (10.8)	<u>0</u>	<u>1</u> (1.4)	<u>17</u> (23.0)	<u>6</u> (8.1)	<u>2</u> (2.7)	<u>1</u> (1.4)
Bruising‡	<u>5</u> (6.8)	<u>3</u> (4.1)	<u>0</u>	<u>1</u> (1.4)	<u>5</u> (6.8)	<u>7</u> (9.5)	<u>0</u>	<u>1</u> (1.4)
Pain‡	<u>14</u> (18.9)	<u>5</u> (6.8)	<u>2</u> (2.7)	<u>2</u> (2.7)	<u>22</u> (29.7)	<u>5</u> (6.8)	<u>1</u> (1.4)	<u>0</u>
Pruritus‡	<u>4</u> (5.4)	<u>0</u>	<u>1</u> (1.4)	<u>0</u>	<u>4</u> (5.4)	<u>2</u> (2.7)	<u>0</u>	<u>0</u>
Induration‡	<u>3</u> (4.1)	<u>0</u>	<u>0</u>	<u>1</u> (1.4)	<u>1</u> (1.4)	<u>0</u>	<u>0</u>	<u>0</u>

\* Reactions started between the day of first injection and 13 days after the day of first injection, or before touch-up injection.

† Number of subjects with at least 1 episode of specified duration.

‡ Duration = Maximum number of consecutive days with symptom from onset until resolution.

§ Reactions occurring from the day of injection through Day 13 after the second injection.

Note: The incidence of induration after the second injection was <5% for both test and control devices.

After all patients finished the 12 month follow-up period, each patient was offered a 12 month touch up injection with their choice of either **EVOLENCE®** or HA Control Product. Of the 149 patients enrolled in the study, 123 opted to take advantage of this offer. At that visit, 58 had **EVOLENCE®** injected into their nasolabial folds and 65 had HA Control Product injected into their nasolabial folds. The protocol did not call for any follow-up of these patients; however, at one site the investigator decided to follow-up with a phone call and the safety results for those 17 patients are presented in Table 3 below. None of the adverse events were severe or serious. Of the 58 subjects receiving **EVOLENCE®**, 11 of the 13 subjects for which adverse events were collected (86.4%) experienced a total of 21 adverse events. These adverse events are reported in Table 3, below. As per the protocol, no follow up was done at any of the other four investigational sites, nor were any adverse events spontaneously reported.

**Table 3. Subjects with Adverse Events At 12 Month Optional Touch Up Visit (Solicited By a Single Investigational Site Only)**

	After 12 Month Touch Up Injection (AEs Reported by a Single Investigational Site Only N=17)	
	<b>EVOLENCE® (N = 13)</b>	<b>HA Control Product (N = 4)</b>
No. of Subjects	11 (86.4%)	3 (75%)
No. of Episodes	21	4
Bruising	4 (30.8)	2 (50.0)
Erythema	6 (46.1)	0
Irritation	1 (7.7)	0
Pain	1 (7.7)	1 (25.0)
Pruritis	1 (7.7)	0
Swelling	8 (61.5)	1 (25.0)

The majority of the skin reactions at either the **EVOLENCE®** or the HA Control Product injection sites were of <4 days duration and almost all of them were less than one week in duration. Adverse events that were initially reported at or after Visit 8 and before Visit 10 were considered to be related to **EVOLENCE®** in 2 (1.4%) subjects and to Control Product in 1 (0.7%) subjects. In these subjects small white papules were reported at the injection site.

Non Local Adverse events considered to be non-device related, occurred in 41/149 (27.5%) of the study subjects. Since each subject received both **EVOLENCE®** and HA based control treatment, the causality of these events could not be identified. These events included Infections and Infestation (10.1%) (upper respiratory infection, nasopharyngitis, sinusitis); Skin and Subcutaneous tissue disorder (5.4%) (actinic keratosis); Hypercholesterolemia (2%); Psychiatric disorder (2%)(anxiety).

### Use of EVOLENCE® in Skin of Color Patients

Of the 149 subjects randomized in the US pivotal study, twenty two (22) had skin tones of light brown (Fitzpatrick skin tone IV), six (6) had skin tones of brown (Fitzpatrick skin tone V), and no subjects had skin tone of black (Fitzpatrick skin tone VI). In a separate skin challenge study, two (2) subjects had skin tone of brown (Fitzpatrick skin tone V). Twenty nine (29) subjects in France, Canada and Germany (i.e., twenty eight (28) with FP skin tone V and one with FP skin tone VI) had EVOLENCE® injected in a post marketing setting. None of these subjects experienced hyperpigmentation or keloid formation.

### Skin Challenge Study - Hypersensitivity

In an open-label, non-controlled, single-center study, 530 subjects were injected with two sequential intradermal EVOLENCE® skin test injections (two week interval), to evaluate the risk of developing localized hypersensitivity. Of the 519 subjects that completed the study period, there were no clinical observations of hypersensitivity, as measured by clinical and patient observation of local responses and laboratory measurement of immunological (antibody) responses. (Positive hypersensitivity reaction was defined as erythema persisting more than 72 hours plus positive histopathology biopsy assessment of the site biopsy).

In addition no serious adverse events or unexpected adverse events occurred during the study period. Overall, 62 subjects reported 95 adverse events over the course of the study. 17 of the 95 adverse events were considered related to the treatment. No adverse events resulted in discontinuation from the study participation. All reported adverse events with two or more occurrences in this hypersensitivity study are listed in Table 4.

**Table 4: All Adverse Events Reported on or after One Skin Test Injection in >1 Subject (n=530)**

Description of AE	Number	Frequency (%)
Headache	8	1.5
Injection Site Erythema	5	0.9
Injection Site Discomfort	6	1.1
Injection Site Pruritus	6	1.1
Nasopharyngitis	5	0.9
Pharyngeal Pain	3	0.6
Nasal congestion	3	0.6
Dizziness	3	0.6
Influenza	3	0.6
Myalgia	2	0.4
Sinusitis	2	0.4
Cystitis	2	0.4
Cough	2	0.4
Pryexia	2	0.4
Joint injury/sprain	2	0.4
Vomiting	2	0.4
Contact dermatitis	2	0.4

Contusion	2	0.4
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Related adverse events occurring in a single patient included swelling, injection site discoloration and injection site irritation. Other events occurring in a single patient, included injection site anaesthesia, fatigue, tenderness, aches, pains, sprains, injuries, anxiety, heart rate increase, herpes zoster, hyperhidrosis, ear infection, bronchitis, tooth infection, nausea, migraine, rash, increased tear production, ocular redness, and outpatient non-related surgical procedures.

One subject experienced erythema, tenderness and induration at the second skin test site (right forearm) more than two months post the End of the Study (more than three months after dosing of the second skin test). Histopathology from the biopsy site indicated that a positive hypersensitivity reaction was occurring. No sequelae were noted at the first skin test site (left forearm). Sera from this subject displayed positive titers for porcine collagen at study baseline prior to **EVOLENCE**<sup>®</sup>-Test injection and titers of sera from this subject remained positive up to the end of the study.

### **Potential Adverse Events**

In post marketing safety analyses of **EVOLENCE**<sup>®</sup> from US, EU and other countries, one inflammatory adverse event (acneform cyst in one individual) and necrosis (2 events) have been reported. Other than these reported adverse events, none of the reported adverse events were greater in severity or duration, required new treatments for resolution or were adverse events not previously observed in the pivotal clinical study described below. Reported treatments have included oral and topical antibiotics and oral steroids. Duration of the majority of these effects resolved within 2 weeks.

In addition to the postmarket surveillance, there have been no Medical Device Reports or evidence of adverse events from the ongoing postapproval study of Evolence in the United States.

## **CLINICAL STUDIES**

### **a) Pivotal Study**

#### **Study Design:**

“A randomized, comparative, multi-center, within subject (split-face) clinical trial was conducted to compare the safety and efficacy of **EVOLENCE**<sup>®</sup> Collagen Filler versus Control ([HA Control Product]) for the correction of soft tissue contour deficiencies.”

Subjects were screened and tested for hypersensitivity to porcine collagen by injecting 0.1 mL of **EVOLENCE**<sup>®</sup>-Test. Subjects with a positive reaction within approximately 4 weeks of the injection were to be discontinued from the study. Blood samples were collected prior the treatment and during follow up visits for determination of collagen antibody titers.

Eligible subjects meeting all inclusion/exclusion criteria were randomized and received injections of investigational device and comparator into their nasolabial folds. Each subject was injected with **EVOLENCE**<sup>®</sup> into one nasolabial fold (NLF)

and Hyaluronic Acid-based dermal filler (HA Control Product) into the contralateral NLF.

Treatment was considered to be complete when Optimal Cosmetic Result (OCR) was achieved, as determined by the judgment of the Principal Investigator. Subjects could receive one touch-up injection with either **EVOLENCE**<sup>®</sup> or the Control 2 weeks later in order to achieve OCR.

The OCR evaluation for both sides was approximately 2 weeks after the initial injection if no touch-up had been given, or 1 week after the touch-up injection. The OCRs evaluation was performed on both sides at the same time. Routine follow up visits for safety and effectiveness occurred at 3 month intervals post OCR visit through 12 months follow-up after the last treatment.

Adequacy of masking of the subject and the Blinded Evaluating Investigator (BEI) was checked following each facial injection, and at 6 and 12 months post OCR visit. Standardized facial photography was taken prior to treatment and during the study follow up. The BEI evaluated the severity of the subjects NLF's using a validated 7-point photographic grading scale Modified Fitzpatrick Wrinkle Scale (MFWS). BEI and subject self satisfaction with the overall treatment response using the Global Improvement Assessment scale (GIA), ranging from 1=much better to 4=worse, after each injection session and at each follow-up visit was conducted.

#### Study End points:

The primary efficacy endpoint for the study of **EVOLENCE**<sup>®</sup> for the correction of the nasolabial folds was compared to the control, as determined by BEI's live evaluation of the NLF severity score (utilizing MFWS) at the 6-month post-OCR visit. The statistical objective was to demonstrate non-inferiority of the **EVOLENCE**<sup>®</sup> to the study control. Efficacy assessments were performed after each injection, at the time of OCR visit, and at 3, 6, 9, and 12 months following the OCR visit. Efficacy assessments at the 9 and 12 month timepoints addressed **EVOLENCE**<sup>®</sup> only and were designed to determine the continued efficacy of **EVOLENCE**<sup>®</sup> and the observed treatment effect through 12 months post-OCR. The 9 and 12 month assessments were not performed for the study control.

Safety was evaluated by comparing the incidence and severity of local and systemic adverse events reported by the treating investigator from the pretreatment skin testing through the 12-month follow-up post-OCR visit.

Additional analysis included BEI and subject satisfaction (utilizing GIA) with the overall treatment response; measurements of anti-porcine collagen antibodies and comparison of total volume of **EVOLENCE**<sup>®</sup> injected to the NLF to achieve OCR Vs. the study control.

#### Study Population:

A total of 149 (30-74 years of age) subjects were treated; while 148 (99.2%) completed the 6 month follow-up period and 145 (97.3) completed the 12 month follow-up period. Four subjects were discontinued before the last visit: one due to an AE, two were lost of follow-up, and one at the subject's request. Demographics are outlined in table 5 below.

#### **Table 5: Subject Demographics –ITT Population**

	<b>Number (%) of Subjects</b>
	<b>ITT (N = 149)</b>
<b>Gender – n (%)</b>	
Male	12 (8.1)
Female	137 (91.9)
<b>Age (yr)</b>	
Mean ± SD	55.7 ± 8.3
Range	30.4 – 73.8
<b>Race – n (%)</b>	
White	138 (92.6)
Asian	1 (0.7)
Native Hawaiian or other Pacific Islander	0
Black or African American	4 (2.7)
American Indian or Alaska Native	0
Other	6 (4.0)
<b>Ethnicity – n (%)</b>	
Hispanic/Latino	18 (12.1)
Not Hispanic/Latino	131 (87.9)
<b>Skin Tone – n (%)</b>	
I to III Pale White/White	121 (81.2)
IV Light brown	22 (14.8)
V Brown	6 (4.0)
VI Black	0
<b>Mean pretreatment MFWS Severity Score</b>	
<b>EVOLENCE<sup>®</sup></b>	2.38
Restylane <sup>®</sup>	2.37

**Efficacy Results:**

**EVOLENCE<sup>®</sup>** was found to be non inferior to the study control in the correction of NLF. During the 6 month follow up there was no statistically significant difference between **EVOLENCE<sup>®</sup>** and the HA Control Product with regard to the measure of improvement at any time point (See Table 6). **EVOLENCE<sup>®</sup>** also was demonstrated to provide substantial correction from baseline at the 9 and 12 month OCR visits, although there was some reduction from OCR.

**Table 6: Change in Modified Fitzpatrick Wrinkle Scale (MFWS) – Blinded Evaluating Investigator’s Assessment – ITT Population (n=149)**

	<b>EVOLENCE<sup>®</sup></b>	<b>HA Control Product</b>	<b>Difference</b>
<b>Screening</b>			
N	149	149	149
Mean ± SD	2.38 ± 0.36	2.37 ± 0.36	0.01 ± 0.30
<b>OCR Visit</b>			
Mean ± SD	0.53 ± 0.52	0.50 ± 0.48	0.03 ± 0.35
<b>Change from Screening at OCR</b>			

Mean ± SD	-1.85 ± 0.50	-1.87 ± 0.45	0.02 ± 0.41
<b>Observed Value at 3 months</b>			
Mean ± SD	0.76 ± 0.65	0.71 ± 0.62	0.05 ± 0.48
<b>Change from Screening at 3 months</b>			
Mean ± SD	-1.62 ± 0.56	-1.66 ± 0.55	0.04 ± 0.48
<b>Observed Value at 6 months</b>			
Mean ± SD	0.92 ± 0.65	0.87 ± 0.69	0.05 ± 0.53
<b>Change from Screening at 6 months</b>			
Mean ± SD	-1.46 ± 0.57	-1.50 ± 0.60	0.04 ± 0.52
Observed Value at 9 months			
Mean ± SD	1.27 ± 0.65	N/A	N/A
Change from Screening at 9 months			
Mean ± SD	-1.11 ± 0.55	N/A	N/A
Observed Value at 12 months			
Mean ± SD	1.59 ± 0.67	N/A	N/A
Change from Screening at 12 months			
Mean ± SD	-0.79 ± 0.62	N/A	N/A

SD= standard deviation; Ranged from 0=No wrinkle – 3=Deep wrinkle

N/A= Not Applicable. Assessments beyond 6 months were made only for EVOLENCE® to determine 12 months efficacy.

**Table 7: EVOLENCE® Efficacy at 9 and 12 Months Based on Blinded Evaluating Investigator’s Assessment of MFWS – ITT Population**

<b>Number (%) of Subjects with EVOLENCE® Correction from Baseline &gt; 0.5 on MFWS</b>	<u>9 Months</u>	<u>12 Months</u>
Total ITT Population	N = 149	N = 149
Number (%)	142 (95.3)	114 (76.5)
Subjects With Touch-up Injection	N = 72	N = 72
Number (%)	70 (97.2)	55 (76.4)
Subjects Without Touch-up Injection	N = 77	N = 77
Number (%)	72 (93.5)	59 (76.6)

**EVOLENCE®** efficacy at 9 and 12 months is provided in Table 6 for the ITT population and is shown for subjects who did and did not receive touch-up injections. At 9 months post-OCR visit and at 12 months post-OCR visit 95.3% and 76.5% of the 149 subjects (respectively) exhibited improvement from baseline at least 0.5 on the MFWS of **EVOLENCE®**. In the 72 subjects who received touch up injection, 70 (97.2%) and 55 (76.4%) exhibited **EVOLENCE®** efficacy at 9 months post OCR and at the 12 months post-OCR, respectively. The results in 77 subjects who did not receive a touch-up injection were similar to those subjects who had touch-up injection: 72 (93.5%) and 59 (76.6%) exhibited **EVOLENCE®** efficacy at 9 months post OCR and at the 12 months post-OCR, respectively. ColBar concludes from these

data that the correction obtained with **EVOLENCE**<sup>®</sup> was effective for up to 12 months following the OCR visit. Furthermore, a similar efficacy rate was observed whether or not subjects underwent touch-up injections.

#### Antibody Testing:

The ELISA results indicate that multiple injections of **EVOLENCE**<sup>®</sup> for test and treatment did not result in development of antibodies against porcine type I collagen during this study of any clinical significance. With respect to IgG titers, 117 (80%) of the subjects were negative at all time points. Thirteen (8.8%) of the subjects displayed positive titers at both the Enrollment and Follow Up Visits of the study. Ten (6.8%) of the subjects changed status from negative to positive titers during the study. Three subjects (2%) were borderline at enrollment and remained borderline at the end of the study and 1 subject (0.7%) changed from borderline to positive.

Notably the 14 subjects with elevated titers of antibodies to porcine collagen did not display any unusual adverse events with respect to incidence or characteristics, or any evidence of clinical symptoms compared to the general patient population. Of the 14 subjects with elevated titers post treatment, 10 subjects experienced adverse events at the injection site. These injection site adverse events were reported for both the **EVOLENCE**<sup>®</sup> injection site and the HA Control product injection site. This proportion of adverse events (10/14, 71%) is similar to that observed in the entire **EVOLENCE**<sup>®</sup> population (126/149, 84.6%). All reactions observed in the 10 subjects with elevated titers were mild in severity and transient.

Twenty five subjects had elevated titers for one or more immunoglobulins at the 6 months post-OCR visit. Samples from all these subjects were obtained at 12 months post-OCR visit. Two subjects demonstrated an increase on IgE titers between 6 and 12 months. Specifically, Subject 02/004 demonstrated an increase in titer from 1:640 to 1:1280, while Subject 04/017 exhibited a titer of 1:160 at the 10 month time point (whereas this subject had not had a positive titer at any prior time point). No increases greater than 1 sample dilution were observed for any subjects for IgG, IgM, or IgA antibodies. There were no adverse events reported for any subject with detectable anti-porcine titers, irrespective of changes observed between the 6 and 12 month time points.

#### **b) Skin Challenge Study of Hypersensitivity**

##### Study Design

Prospective open label, non-controlled, single center clinical study with two sequential skin test injections were used to evaluate the risk of developing localized immune hypersensitivity.

In the initial visit baseline blood sample for anti- porcine collagen type I antibodies was obtained. The second visit consisted of the first skin test (0.1mL of **EVOLENCE**<sup>®</sup> -Test injected intradermally in the mid-volar, left forearm) to produce a bleb. Subjects then returned in approximately 72 hours for an evaluation of the skin test. All subjects who proved non-reactive to the first skin test were injected with a second skin test in the contra-lateral volar forearm after approximately 14 days. Approximately 72 hours after second injection, subjects returned for evaluation of the

skin test sites and they returned again after ~30 days for evaluation. A second and final blood sample for anti- porcine collagen type I antibodies was taken at the final visit. The tested sites were monitored daily by the subject for signs of systemic and local reactions.

Healthy volunteers (18 years of age or older) were enrolled. Main exclusion criteria were: pregnant and/or nursing subjects; subjects treated with chemotherapy agent or systemic corticosteroids within the past 3 months; subjects with known allergy to collagen; subjects with a history of autoimmune disorder; subjects with severe allergies manifested by a history of anaphylaxis; or subjects with a current disease state that can affect immune response.

### Study Objectives

The purpose of this study was to demonstrate that the risk of experiencing hypersensitivity to a double skin test with porcine collagen implants was less than 1.3%. A risk of 1.3% - 1.5% is the estimated risk of developing hypersensitivity complications during facial treatments with injectable bovine collagen for subjects who were initially negative to the bovine collagen skin test.

### Study Population

Fife hundred and thirty (530) subjects were enrolled into the study consisting of 104 males and 426 females. The subjects' ages ranged from 18 to 92. 519 subjects completed the study and were included in the evaluable population. 530 subjects were included in the safety population evaluation. In this study two (2) subjects had skin tone of brown (Fitzpatrick skin tone V).

### Results

Of the subjects who received 2 sequential skin tests, no subject displayed a positive hypersensitivity response against **EVOLENCE**<sup>®</sup>-Test (erythema grade moderate or severe reaction). All subjects who displayed mild and mild to moderate erythema and did not exceed the initial bleb size of the implanted **EVOLENCE**<sup>®</sup>-Test. No induration was observed.

### Post Study Observation:

One subject displayed delayed local positive hypersensitivity reaction of increasing redness, swelling and tenderness at the right volar forearm (2<sup>nd</sup> injection site) more than two months post the end of the study (more than 3 months after injection of the second **EVOLENCE**<sup>®</sup> skin test).

### Conclusions:

No instance of hypersensitivity was observed during the study period. The upper bound of the one-sided exact 95% confidence interval for subjects experiencing strong to severe reactions to the **EVOLENCE**<sup>®</sup> skin test is 0.58%. Based on these findings no pre-treatment skin testing is required.

## **DIRECTIONS FOR USE**

**EVOLENCE**<sup>®</sup> Collagen Filler is an injectable product indicated for the correction of moderate to deep facial wrinkles and folds such as nasolabial folds.

### **Assembly of Needle to Syringe:**

For safe use of **EVOLENCE**<sup>®</sup> it is important that the needle is properly assembled onto the syringe. Use the 27GX1/2" needle provided.

1. Carefully unscrew the syringe tip cap while securely holding the syringe Luer adapter.
2. With a loose grip on the narrow part of the needle shield, mount the needle on the Luer-syringe lock by screwing clockwise until counter pressure is felt.
3. With a firm grip on the wider part of the needle shield, press and turn the needle further until secure (approximately a quarter turn).
4. Remove the needle shield by pulling the shield straight away from the syringe, ensuring not to twist the shield during removal.

#### **Injection of EVOLENCE<sup>®</sup> Collagen Filler:**

1. Prior to treatment with **EVOLENCE**<sup>®</sup> the patient should be fully apprised of the indications, contraindications, warnings, precautions, adverse events and method of administration. A complete medical history should be obtained to ensure suitability for treatment. Patient also should be advised that a supplemental "touch-up" injection may be required to achieve and maintain optimal correction.
2. The patient's wrinkle or fold should be characterized with regard to etiology, distention, stress at site and depth of lesion. Pretreatment photographs are recommended.
3. Topical and/or injectable anesthesia may be used to manage pain during and after injection.
4. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or another antiseptic substance.
5. Before injecting the patient, depress the plunger until the product flows out of the needle.
6. The needle should be placed in a sterile manner into the plane(s) of apparent deformity.
7. The injection technique of **EVOLENCE**<sup>®</sup> with regard to the angle and orientation of the bevel, the depth of injection and the quantity administered may vary. A linear threading technique, tunneling technique, serial puncture injections or combinations have been used to achieve optimal results.
8. For linear threading technique and/or tunneling technique the needle is inserted at an approximate angle of 30<sup>0</sup> parallel to the length of the wrinkle or fold. The bevel of the needle should face upward and the substance should be injected into the mid to deep dermis. This can be ascertained by observing a subtle elevation of the defect without any blanching following injection.
9. If **EVOLENCE**<sup>®</sup> is injected too superficially this may result in visible lumps and or discoloration.
10. Inject **EVOLENCE**<sup>®</sup> by applying even pressure on the plunger rod while slowly pulling the needle backwards. The wrinkle should be lifted and eliminated by the end of the injection. It is important that the injection is stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.

11. Correct to 100% of the desired contour effect. Do not overcorrect.  
With cutaneous contour deformities the best results are obtained if the defects can be manually stretched to the point where it is eliminated. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the injected site, the depth of the implant in the tissue and the injection technique.
12. If immediate blanching occurs, this could be an indication that the device injection is too superficial. The injection should be stopped and the area massaged until it returns to a normal color. When the injector continues treatment, they should assure that the appropriate injection depth is reached.
13. When injection is complete, the treated side should be gently massaged so it conforms to the contour of the surrounding tissues. In the event of unintentional overcorrection, massage the area firmly between your fingers or against an underlying superficial bone to obtain optimal results.
14. Needles may become occluded or dull during a treatment session, and needle replacement may be necessary.
15. With patients who have localized swelling, the degree of correction is sometime difficult to judge at the time of treatment. In this case it is better to invite the patient to a touch-up session after 1-2 weeks. Although the company has not observed severe reactions during treatment in the 668 subjects injected in the US **EVOLENCE**<sup>®</sup> clinical trials, in the event that severe swelling or a systemic reaction occurs during injection, discontinue treatment and contact OrthoDermatologics (1-800- 386-5362).
16. Corrective touch up injection may be required to achieve optimal correction of the contour. If the deformity needs further treatment the same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as deformity severity, skin elasticity and dermal thickness at the treatment site.
17. Patients may have mild to moderate injection site reactions, which typically resolved in a few days.
18. Severely indurated defects which initially resist distention may require several treatment sessions before desired correction is obtained. In such defects, it is preferable to fill within the indurated defect rather than beneath it.
19. The physician should instruct the patient to report any problems possibly associated with the use of **EVOLENCE**<sup>®</sup>.

## **PATIENT INSTRUCTIONS**

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

- Within the first 24-48 hours patients should avoid :
  - Strenuous exercise
  - Excessive sun, extreme heat, or extreme cold exposure
  - Alcoholic beverages

Exposure to any of the above may cause temporary redness, swelling and/or itching at the injection sites.

- To report an adverse reaction, call OrthoDermatologics (1-800- 386-5362).

## HOW SUPPLIED

**EVOLENCE**<sup>®</sup> Collagen Filler is supplied in single use glass syringe with a luer- lock fitting. The product is presented as a sterile, non-pyrogenic gel in 1.0 mL syringe. Fill volume varies between presentation and is stated on the syringe label and carton.

Sterilized needles 2X 27GX 1/2" are packed beneath the transparent blister insert. In order to use the needles, gently pull up the insert and expose the needle pack beneath it. Three patient record labels are provided. Do not use if package is opened or damaged.

### STERILE NEEDLES

- Follow national, local or institutional guidelines for use and disposal of medical sharp devices. Obtain prompt medical attention if injury 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 reshield used needles. Recapping by hand is a hazardous practice and should be avoided.

## STORAGE

- **EVOLENCE**<sup>®</sup> should be stored at room temperature, between 59<sup>0</sup>F-86<sup>0</sup>F (15<sup>0</sup>C-30<sup>0</sup>C). Avoid refrigeration and freezing. Protect from sunlight.
- **EVOLENCE**<sup>®</sup> is a yellowish, homogenous, opaque gel. In the event that a syringe contains material exhibiting separation between solid and liquid, or change of color, do not use the syringe and notify OrthoNeutrogena immediately at 1-800- 386-5362.

## STERILITY

**EVOLENCE**<sup>®</sup> Collagen Filler collagen filler is for single use only. The content of the syringe is manufactured by validated aseptic production processes and should be used immediately after opening. Discard any unused **EVOLENCE**<sup>®</sup>. The needles supplied with the package are sterile.

Sterility is maintained only if the syringe and packaging of the needles are intact and undamaged.

### Symbols



Attention, see instructions for use



Do not reuse



Use by/Expiration Date



Lot/Batch number



Processed using aseptic process;

Only the content of the syringe is sterile



Temperature limitation

**REF**

Catalogue number

**MANUFACTURED BY:**  
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