EVOLYSSE™ FORM Directions for Use

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

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

EVOLYSSE™ FORM is a sterile, bioabsorbable, colorless gel implant containing 22 mg/mL of hyaluronic acid with 3 mg/mL lidocaine hydrochloride in physiologic buffer. The hyaluronic acid is produced by *Streptococcus* species of bacteria and is crosslinked with 1,4-butanediol diglycidyl ether (BDDE). EVOLYSSE™ FORM contains the local anesthetic lidocaine to reduce pain and improve comfort during and post-injection.

2. INTENDED USE/INDICATIONS

EVOLYSSE™ FORM is indicated for dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in adults 22 years and older.

3. CONTRAINDICATIONS

- EVOLYSSE™ FORM is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- EVOLYSSE™ FORM may contain trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- EVOLYSSE™ FORM contains lidocaine and is contraindicated for patients with a history of allergies to such material.

4. WARNINGS

Before use, the following warnings must be considered. The healthcare professional must comply fully with the instructions given in Section 8 INSTRUCTIONS FOR USE.

- The product must not be injected into blood vessels. Introduction of EVOLYSSE™ FORM into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting the product. For example, after insertion of the needle and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate healthcare specialist should an intravascular injection occur (see INSTRUCTIONS FOR USE – *Injection Technique #6*).

- Defer use of EVOLYSSE™ FORM at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the underlying process has been controlled.

5. PRECAUTIONS

- EVOLYSSE™ FORM is for single use only and should be discarded immediately after use. Do not resterilize. Do not use if package is opened or damaged.
- EVOLYSSE™ FORM is a smooth, colorless gel. If the syringe contents show signs of separation and/or appear cloudy, do not use the syringe, and contact Evolus Customer Experience at 877-386-5871.
- This product should only be used by healthcare professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the injection site to minimize the risks of potential complications (perforation or compression of vessels, nerves, and other vulnerable structures).
- Healthcare professionals must discuss all potential risks of soft tissue filler injections with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- EVOLYSSE™ FORM is intended for dermal and subdermal injections to correct dynamic facial wrinkles and folds. The safety and effectiveness of other treatment areas have not been established in controlled clinical studies.
- The safety for use in sites with proximity to other implants (including permanent implants) has not been studied.
- Injection of EVOLYSSE™ FORM into patients with a history of previous facial herpetic eruption may be associated with reactivation of the herpes.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, or pigmentation disorders has not been studied.
- EVOLYSSE™ FORM should be used with caution in patients with an autoimmune disorder or on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at injection sites.
- As with all transcutaneous procedures, soft tissue filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- If laser treatment, chemical peeling, or any other procedure based on an active dermal response is considered after treatment with EVOLYSSE™ FORM, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if EVOLYSSE™ FORM is administered before the skin has healed completely after such procedures.
- Patients may experience late onset adverse events with the use of soft tissue fillers, including EVOLYSSE™ FORM.
- The product contains lidocaine. If other local anesthetics or agents structurally related to amide-type local anesthetics are used concurrently with the product, the following considerations should be observed:
    - Use with caution in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction

    - High doses of lidocaine (more than 200 mg/day) can cause acute toxic reactions manifesting as symptoms affect the central nervous system and cardiac conduction
- EVOLYSSE™ FORM 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.
- Injection of EVOLYSSE™ FORM too superficially and injection in facial areas with limited soft tissue support or soft tissue cover, or thin skin, may result in skin contour irregularities and palpable lumps and/or bluish discoloration.
- Patients should be advised to minimize exposure of the treated area to extreme temperatures (e.g., intense cold or sauna) until any local inflammation has resolved.
- After use, syringes and needles should be handled as potential biohazards. Handle and dispose in accordance with accepted medical practice and applicable local, state, and federal requirements.

6. ADVERSE EVENTS

A. US Pivotal Study CLIN2101 for Facial Wrinkles and Folds

In the multicenter, double blind, randomized, controlled clinical trial conducted to evaluate the safety and effectiveness of EVOLYSSE™ FORM versus a control treatment for the correction of nasolabial folds (NLFs), 70 subjects were randomized and treated with EVOLYSSE™ FORM in one NLF and the control in the contralateral NLF. Touch-up treatments were offered two weeks after initial treatment. All subjects were offered an optional retreatment with EVOLYSSE™ FORM for both NLFs at 12 months and a retreatment touch-up 2 weeks later, if needed; 47 subjects elected to receive retreatment.

Subjects used preprinted diary forms to record specific signs and symptoms of common treatment responses (CTRs) experienced during the 30 days after initial treatment and retreatment (if performed). Subjects were instructed to rate each CTR listed on the diary as Mild, Moderate, Severe, or None.

- None or not applicable.
- Mild CTRs were defined as signs and symptoms that can be easily tolerated, can be ignored and disappear when distracted.
- Moderate CTRs were defined as signs and symptoms that cause discomfort and interfere with normal functioning but are tolerable and cannot be ignored and do not disappear when distracted.
- Severe CTRs were defined as signs and symptoms that affect usual daily activity and incapacitate, thereby interrupting daily activities.

The severity and duration of CTRs reported by >5% of subjects after initial treatment are summarized in Table 1 and Table 2, respectively. The incidence and severity of CTRs were similar between the EVOLYSSE™ FORM and control NLFs with most CTRs reported as mild or moderate and resolving within 7 days. The incidence of CTRs was lower after retreatment with EVOLYSSE™ FORM.

Table 1: Common Treatment Responses by Maximum Severity After Initial Treatment with EVOLYSSE™ FORM and Control Occurring in > 5% of Treated Subjects (N = 66)

CTR	EVOLYSSE™ FORM				Control			
	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Tenderness	75.8% (50)	47.0% (31)	25.8% (17)	3.0% (2)	71.2% (47)	42.4% (28)	25.8% (17)	3.0% (2)
Swelling	69.7% (46)	40.9% (27)	27.3% (18)	1.5% (1)	69.7% (46)	48.5% (32)	19.7% (13)	1.5% (1)
Bruising	60.6% (40)	27.3% (18)	28.8% (19)	4.5% (3)	56.1% (37)	30.3% (20)	24.2% (16)	1.5% (1)
Redness	57.6% (38)	34.8% (23)	19.7% (13)	3.0% (2)	48.5% (32)	27.3% (18)	21.2% (14)	0
Lumps	57.6% (38)	28.8% (19)	24.2% (16)	4.5% (3)	54.5% (36)	30.3% (20)	22.7% (15)	1.5% (1)
Pain	53.0% (35)	34.8% (23)	16.7% (11)	1.5% (1)	50.0% (33)	34.8% (23)	15.2% (10)	0
Discoloration	36.4% (24)	18.2% (12)	15.2% (10)	3.0% (2)	33.3% (22)	16.7% (11)	16.7% (11)	0
Itching	28.8% (19)	21.2% (14)	6.1% (4)	1.5% (1)	31.8% (21)	27.3% (18)	4.5% (3)	0
Headache	6.1% (4)	6.1% (4)	0	0	6.1% (4)	6.1% (4)	0	0

Table 2: Common Treatment Responses by Duration After Initial Treatment with EVOLYSSE™ FORM and Control Occurring in > 5% of Treated Subjects (N = 66)

CTR	EVOLYSSE™ FORM					Control				
	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)
Tenderness	47.0% (31)	15.2% (10)	12.1% (8)	1.5% (1)	0	47.0% (31)	13.6% (9)	9.1% (6)	1.5% (1)	0
Swelling	33.3% (22)	27.3% (18)	7.6% (5)	1.5% (1)	0	39.4% (26)	21.2% (14)	9.1% (6)	0	0
Bruising	18.2% (12)	21.2% (14)	18.2% (12)	1.5% (1)	1.5% (1)	15.2% (10)	21.2% (14)	18.2% (12)	1.5% (1)	0
Redness	33.3% (22)	10.6% (7)	13.6% (9)	0	0	25.8% (17)	12.1% (8)	10.6% (7)	0	0
Lumps	24.2% (16)	3.0% (2)	16.7% (11)	10.6% (7)	3.0% (2)	28.8% (19)	9.1% (6)	10.6% (7)	3.0% (2)	3.0% (2)
Pain	36.4% (24)	9.1% (6)	7.6% (5)	0	0	31.8% (21)	12.1% (8)	6.1% (4)	0	0
Discoloration	12.1% (8)	9.1% (6)	13.6% (9)	1.5% (1)	0	13.6% (9)	9.1% (6)	9.1% (6)	1.5% (0)	0
Itching	15.2% (10)	9.1% (6)	1.5% (1)	3.0% (2)	0	21.2% (14)	9.1% (6)	1.5% (1)	0	0
Headache	6.1% (4)	0	0	0	0	6.1% (4)	0	0	0	0

An Adverse Event (AE) was defined as an untoward medical occurrence which did not necessarily have a causal relationship to the study device. The AE was considered related to the study device if a causal relationship was at least a reasonable possibility.

Of the 70 treated, 11 subjects (14.3%) had 18 treatment-related AEs in the EVOLYSSE™ FORM NLF and 8 subjects (8.6%) had 13 treatment-related AEs in the control NLF after initial treatment. Most AEs were mild, required no action to be taken, resolved within 2 months. The most common treatment-related AEs in the EVOLYSSE™ FORM NLF were injection site mass (6 subjects), injection site discoloration, injection site pain, and injection site pruritis (2 subjects each). Injection site swelling, injection site bruising, facial discomfort, sensation of a foreign body, headache, and skin swelling were also reported in 1 subject each. The incidence of treatment-related AEs was higher after treatment with EVOLYSSE™ FORM using 27G needles (22.0%, 9/41) versus 30G needles (7.0%, 3/43). Among the 47 subjects who received retreatment with EVOLYSSE™ FORM, 2 subjects (4.3%) had 2 treatment-related AEs, which included mild injection site pain (1 subject) and mild headache (1 subject) which resolved without any action taken.

There were no treatment-related serious AEs in the study.

7. CLINICAL STUDY

A. US Pivotal Study for Facial Wrinkles and Folds

A multicenter, double blind, randomized, split face, controlled clinical trial was conducted to evaluate the safety and effectiveness of EVOLYSSE™ FORM versus a control treatment for the correction of NLFs. A total of 70 subjects were randomized and treated with EVOLYSSE™ FORM in one NLF and the control in the contralateral NLF. Optional touch-up treatments were administered two weeks after the initial treatment. Routine follow-up visits for safety and effectiveness were conducted at 6 weeks, 3, 6, 9, and 12 months after the initial treatment.

All subjects were offered an optional retreatment with EVOLYSSE™ FORM for both NLFs at 12 months and a retreatment touch-up 2 weeks later, if needed, with the final study visit occurring 3 months after retreatment.

Study Endpoints

The primary effectiveness endpoint was a non-inferiority analysis of EVOLYSSE™ FORM versus control at 6 months based on the validated 5-point Wrinkle Severity Rating Scale (WSRS) scores assigned to photos by an independent photo review (IPR) panel. The primary endpoint used the WSRS in the way in which it was validated (i.e., photo assessments).

Secondary effectiveness endpoints included:

- WSRS responder rates (defined as the percentage of subjects with at least a 1-point improvement since baseline) based on the IPR and blinded live evaluator (BLE) assessments
- Global Aesthetic Improvement Scale (GAIS) responder rates (defined as subjects rated as improved, much improved, or very much improved compared to baseline) based on BLE and subject assessments
- Subject satisfaction based on the validated FACE-Q Appraisal of Nasolabial folds questionnaire

Subject Demographics
Subject demographics and pretreatment characteristics are presented in Table 3 below.

Table 3: Subject Demographics and Pretreatment Characteristics

Demographic/Characteristic	N = 70
Age (years)	
Mean	58.8
Min, Max	25-83
Gender	
Female	66 (94.3%)
Male	4 (5.7%)
Race	
White	51 (72.9%)
Black/African American	14 (20.0%)
Other	2 (2.9%)
Asian	2 (2.9%)
Multiple	1 (1.4%)
Ethnicity	
Hispanic or Latino	21 (30.0%)
Not Hispanic or Latino	49 (70.0%)
Fitzpatrick Skin Type	
I	2 (2.9%)
II	19 (27.1%)
III	22 (31.4%)
IV	16 (22.9%)
V	9 (12.9%)
VI	2 (2.9%)
Median Baseline WSRS Score	
EVOLYSSE™ FORM	3
Control	3

Effectiveness Results
The primary endpoint was met. Based on the IPR results using the WSRS, the difference in change from baseline was in favor of EVOLYSSE™ FORM versus control at 6 months, -0.3 (95% CI [-0.500, -0.032]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001. The IPR responder rates at 6 months for Evolysse™ FORM and control are shown Table 4.

Table 4: WSRS IPR Responder Rates at Month 6

Evolysse™ FORM	Control
45.2% (28/62)	38.7% (24/62)

Throughout the 12-month follow-up period (Table 5), EVOLYSSE™ FORM continued to provide a clinically significant improvement in wrinkle severity with most NLFs maintaining improvement through 12 months [72.1% (44/61)] based on BLE assessments.

At Month 6, the GAIS responder rate was 95.2% (60/63) based on BLE assessments and 88.3% (56/63) based on the subject assessments. At 1 year, the BLE GAIS responder rate was 73.8% (45/61) and the subject GAIS responder rate was 80.3% (49/61).

Table 5: Effectiveness Results through 1 Year (mITT)

Visit	BLE WSRS Responder Rate % (n/N)	GAIS Responder Rate % (n/N)	
		BLE	Subject
Month 3	95.4% (62/65)	96.9% (63/65)	95.4% (62/65)
Month 6	92.1% (58/63)	95.2% (60/63)	88.9% (56/63)
Month 9	83.1% (49/59)	83.1% (49/59)	83.3% (50/60)
Month 12	72.1% (44/61)	73.8% (45/61)	80.3% (49/61)

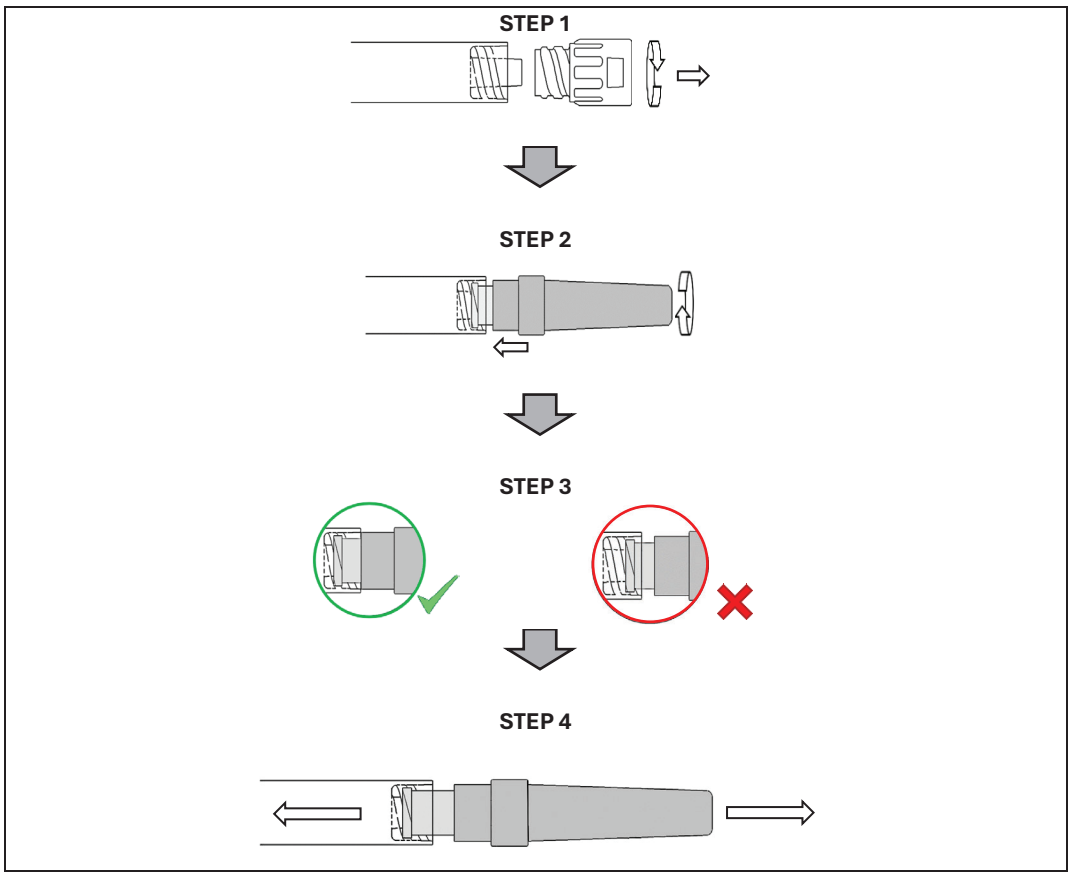
The mean score on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire for the EVOLYSSE™ FORM group improved from 31.5 at baseline to 65.4 at 6 months and 52.4 at 12 months. These improved scores indicate that subjects were satisfied with the appearance of their NLFs after treatment with EVOLYSSE™ FORM compared to baseline.

8. INSTRUCTIONS FOR USE

Pre-Treatment Guidelines

1. Prior to treatment, the subject's medical history should be obtained, and the subject should be fully apprised of the indications, contraindications, warnings, precautions, potential outcomes, adverse events, and method of administration.
2. Use the needles supplied with the syringe.
3. Attach the needle to the syringe, as shown in Figure 1, and according to the following instructions. Only the needles provided with EVOLYSSE™ FORM should be used for injection.
   - Use medical gloves.
   - Carefully remove the stopper from the syringe (step 1).
   - Insert the hub of the needle into the syringe tip and turn it clockwise (step 2).
   - Firmly screw the needle onto the tip of the syringe, holding it by its shield. Continue to tighten the needle until it is seated in the proper position (step 3). If the needle is not properly screwed into position, it may disconnect or result in leakage of the gel.
   - Remove the needle shield just before injection and after skin disinfection (step 4).

Figure 1: Attachment of the Needle to the Syringe



4. Cleanse the area to be treated with a suitable antiseptic solution (without quaternary ammonium compounds).
5. To avoid breakage of the needle, do not attempt to bend or manipulate it before or during injection.
6. Before injecting the gel, press the plunger rod slowly until a small droplet is visible at the tip of the needle.

Injection Technique

1. EVOLYSSE™ FORM is injected into the dermis and/or subdermis using the supplied 30G ½" and/or 27G ½" needles for versatility in treating dynamic wrinkles and folds.
2. Aspiration is recommended prior to implantation to avoid inadvertent injection into a blood vessel.
3. The injection technique may vary in angle and orientation of the needle bevel, injection depth, and quantity administered. The injection techniques used in the pivotal clinical study included retrograde and antegrade linear threading, crosshatching, and serial puncture to achieve optimal results.
4. Inject the gel slowly by gently pressing down on the plunger rod. If the needle is obstructed, do not increase the pressure with the tip of the plunger. Stop the injection and use a new needle.
5. Inject to the desired volume effect for optimal correction. Do not overcorrect. In the pivotal clinical study, the average injection volume to achieve optimal outcomes was 1.2 mL per NLF

(range 0.2-3.0 mL). The mean injection volume per NLF was 0.8 mL at initial treatment, 0.5 mL at touch-up treatment, and 0.8 mL at retreatment.

6. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
7. After injecting the gel, the treated area may be gently massaged.
8. The syringe and needles must be discarded immediately after use in accordance with accepted medical practice and applicable local, state, and federal requirements.

9. HOW SUPPLIED

The gel is supplied sterile in a 1 mL plastic syringe assembled with a plunger rod and finger rest. Sterile 30G ½" and 27G ½" ultra-thin wall needles are provided for injection. EVOLYSSE™ FORM and the needles are for single use only.

10. STORAGE

Store at room temperature (up to 25°C/77°F). Protect from sunlight. Do not freeze.

11. SHELF-LIFE

The expiration date of the device is printed on the label. Do not use after the expiration date.

12. SYMBOLS



Catalog Number



Unique Device Identifier



Lot/Batch Number


Expiration Date (YYYY-MM-DD)



Steam Sterilized

www.evolus.com

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Manufactured by:
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EVOLYSSE™ is a trademark of Evolus, Inc.

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Version 1.0
02/2025

EVOLYSSE™ SMOOTH Directions for Use

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1. DEVICE DESCRIPTION

EVOLYSSE™ SMOOTH is a sterile, bioabsorbable, colorless gel implant containing 20 mg/mL of hyaluronic acid with 3 mg/mL lidocaine hydrochloride in physiologic buffer. The hyaluronic acid is produced by *Streptococcus* species of bacteria and is crosslinked with 1,4-butanediol diglycidyl ether (BDDE). EVOLYSSE™ SMOOTH contains the local anesthetic lidocaine to reduce pain and improve comfort during and post-injection.

2. INTENDED USE/INDICATIONS

EVOLYSSE™ SMOOTH is indicated for dermal and subdermal injection to correct moderate to severe dynamic facial wrinkles and folds (such as nasolabial folds) in adults 22 years and older.

3. CONTRAINDICATIONS

- EVOLYSSE™ SMOOTH is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- EVOLYSSE™ SMOOTH may contain trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- EVOLYSSE™ SMOOTH contains lidocaine and is contraindicated for patients with a history of allergies to such material.

4. WARNINGS

Before use, the following warnings must be considered. The healthcare professional must comply fully with the instructions given in Section 8 INSTRUCTIONS FOR USE.

- The product must not be injected into blood vessels. Introduction of EVOLYSSE™ SMOOTH into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting the product. For example, after insertion of the needle and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate healthcare specialist should an intravascular injection occur (see INSTRUCTIONS FOR USE – *Injection Technique #6*).

- Defer use of EVOLYSSE™ SMOOTH at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present until the underlying process has been controlled.

5. PRECAUTIONS

- EVOLYSSE™ SMOOTH is for single use only and should be discarded immediately after use. Do not resterilize. Do not use if package is opened or damaged.
- EVOLYSSE™ SMOOTH is a smooth, colorless gel. If the syringe contents show signs of separation and/or appear cloudy, do not use the syringe, and contact Evolus Customer Experience at 877-386-5871.
- This product should only be used by healthcare professionals who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the injection site to minimize the risks of potential complications (perforation or compression of vessels, nerves, and other vulnerable structures).
- Healthcare professionals must discuss all potential risks of soft tissue filler injections with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- EVOLYSSE™ SMOOTH is intended for dermal and subdermal injections to correct dynamic facial wrinkles and folds. The safety and effectiveness of other treatment areas have not been established in controlled clinical studies.
- The safety for use in sites with proximity to other implants (including permanent implants) has not been studied.
- Injection of EVOLYSSE™ SMOOTH into patients with a history of previous facial herpetic eruption may be associated with reactivation of the herpes.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 22 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, or pigmentation disorders has not been studied.
- EVOLYSSE™ SMOOTH should be used with caution in patients with an autoimmune disorder or on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at injection sites.
- As with all transcutaneous procedures, soft tissue filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- If laser treatment, chemical peeling, or any other procedure based on an active dermal response is considered after treatment with EVOLYSSE™ SMOOTH, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if EVOLYSSE™ SMOOTH is administered before the skin has healed completely after such procedures.
- Patients may experience late onset adverse events with the use of soft tissue fillers, including EVOLYSSE™ SMOOTH.
- The product contains lidocaine. If other local anesthetics or agents structurally related to amide-type local anesthetics are used concurrently with the product, the following considerations should be observed:
    - Use with caution in patients with epilepsy, impaired cardiac conduction, severely impaired hepatic function, or severe renal dysfunction

    - High doses of lidocaine (more than 200 mg/day) can cause acute toxic reactions manifesting as symptoms affect the central nervous system and cardiac conduction
- EVOLYSSE™ SMOOTH 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.
- Injection of EVOLYSSE™ SMOOTH too superficially and injection in facial areas with limited soft tissue support or soft tissue cover, or thin skin, may result in skin contour irregularities and palpable lumps and/or bluish discoloration.
- Patients should be advised to minimize exposure of the treated area to extreme temperatures (e.g., intense cold or sauna) until any local inflammation has resolved.
- After use, syringes and needles should be handled as potential biohazards. Handle and dispose in accordance with accepted medical practice and applicable local, state, and federal requirements.

6. ADVERSE EVENTS

A. US Pivotal Study CLIN2101 for Facial Wrinkles and Folds

In the multicenter, double blind, randomized, controlled clinical trial conducted to evaluate the safety and effectiveness of EVOLYSSE™ SMOOTH versus a control treatment for the correction of nasolabial folds (NLFs), 70 subjects were randomized and treated with EVOLYSSE™ SMOOTH in one NLF and the control in the contralateral NLF. Touch-up treatments were offered two weeks after initial treatment. All subjects were offered an optional retreatment with EVOLYSSE™ SMOOTH for both NLFs at 12 months and a retreatment touch-up 2 weeks later, if needed; 44 subjects elected to receive retreatment.

Subjects used preprinted diary forms to record specific signs and symptoms of common treatment responses (CTRs) experienced during the 30 days after initial treatment and retreatment (if performed). Subjects were instructed to rate each CTR listed on the diary as Mild, Moderate, Severe, or None.

- None or not applicable.
- Mild CTRs were defined as signs and symptoms that can be easily tolerated, can be ignored and disappear when distracted.
- Moderate CTRs were defined as signs and symptoms that cause discomfort and interfere with normal functioning but are tolerable and cannot be ignored and do not disappear when distracted.
- Severe CTRs were defined as signs and symptoms that affect usual daily activity and incapacitate, thereby interrupting daily activities.

The severity and duration of CTRs reported by >5% of subjects after initial treatment are summarized in Table 1 and Table 2, respectively. The incidence and severity of CTRs were similar between the EVOLYSSE™ SMOOTH and control NLFs with most CTRs reported as mild or moderate and resolving within 7 days. The incidence of CTRs was lower after retreatment with EVOLYSSE™ SMOOTH.

Table 1: Common Treatment Responses by Maximum Severity After Initial Treatment with EVOLYSSE™ SMOOTH and Control Occurring in > 5% of Treated Subjects (N = 64)

CTR	EVOLYSSE™ SMOOTH				Control			
	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)	Total % (n)	Mild % (n)	Moderate % (n)	Severe % (n)
Tenderness	64.1% (41)	48.4% (31)	12.5% (8)	3.1% (2)	65.6% (42)	43.8% (28)	17.2% (11)	4.7% (3)
Swelling	56.3% (36)	32.8% (21)	23.4% (15)	0	62.5% (40)	37.5% (24)	21.9% (14)	3.1% (2)
Lumps	53.1% (34)	32.8% (21)	17.2% (11)	3.1% (2)	59.4% (38)	32.8% (21)	23.4% (15)	3.1% (2)
Bruising	51.6% (33)	28.1% (18)	20.3% (13)	3.1% (2)	54.7% (35)	31.3% (20)	14.1% (9)	9.4% (6)
Redness	51.6% (33)	32.8% (21)	18.8% (12)	0	50.0% (32)	32.8% (21)	12.5% (8)	4.7% (3)
Pain	50.0% (32)	34.4% (22)	15.6% (10)	0	53.1% (34)	34.4% (22)	17.2% (11)	1.6% (1)
Discoloration	40.6% (26)	23.4% (15)	12.5% (8)	4.7% (3)	39.1% (25)	20.3% (13)	12.5% (8)	6.3% (4)
Itching	28.1% (18)	20.3% (13)	7.8% (5)	0	34.4% (22)	21.9% (14)	12.5% (8)	0

Table 2: Common Treatment Responses by Duration After Initial Treatment with EVOLYSSE™ SMOOTH and Control Occurring in > 5% of Treated Subjects (N = 64)

CTR	EVOLYSSE™ SMOOTH					Control				
	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)	< 3 days % (n)	4 – 7 days % (n)	8 – 14 days % (n)	15 – 29 days % (n)	> 30 days % (n)
Tenderness	43.8% (28)	15.6% (10)	3.1% (2)	1.6% (1)	0	39.1% (25)	18.8% (12)	6.3% (4)	1.6% (1)	0
Swelling	31.3% (20)	15.6% (10)	7.8% (5)	1.6% (1)	0	34.4% (22)	15.6% (10)	10.9% (7)	1.6% (1)	0
Lumps	21.9% (14)	17.2% (11)	9.4% (6)	1.6% (1)	3.1% (2)	28.1% (18)	17.2% (11)	6.3% (4)	3.1% (2)	4.7% (3)
Bruising	18.8% (12)	15.6% (10)	12.5% (8)	4.7% (3)	0	21.9% (14)	18.8% (12)	9.4% (6)	4.7% (3)	0
Redness	34.4% (22)	14.1% (9)	0	1.6% (1)	1.6% (1)	35.9% (23)	10.9% (7)	0	3.1% (2)	0
Pain	40.6% (26)	6.3% (4)	3.1% (2)	0	0	39.1% (25)	10.9% (7)	3.1% (2)	0	0
Discoloration	21.9% (14)	6.3% (4)	9.4% (6)	3.1% (2)	0	15.6% (10)	10.9% (7)	7.8% ()5)	4.7% (3)	0
Itching	23.4% (15)	1.6% (1)	3.1% (2)	0	0	28.1% (18)	3.1% (2)	3.1% (2)	0	0

An Adverse Event (AE) was defined as an untoward medical occurrence which did not necessarily have a causal relationship to the study device. The AE was considered related to the study device if a causal relationship was at least a reasonable possibility.

Of the 70 subjects, 5 subjects (7.1%) had 10 treatment-related AEs in the EVOLYSSE™ SMOOTH NLF and 6 subjects (8.6%) had 14 treatment-related AEs in the control NLF after initial treatment. All AEs were mild or moderate and required no action to be taken. Most

AEs resolved within 1 month. The treatment-related AEs in the EVOLYSSE™ SMOOTH NLF were injection site discoloration (3 subjects), injection site mass (2 subjects), injection site erythema (2 subjects), injection site bruising (1 subject), injection site pain (1 subject), and flushing (1 subject). Among the 44 subjects who received retreatment with EVOLYSSE™ SMOOTH, 3 subjects (6.8%) had 5 treatment-related AEs, which included mild injection site bruising (1 subject in both NLFs), swelling (1 subject), pain (1 subject), and mass (1 subject). These AEs all resolved without any action to be taken.

There were no treatment-related serious AEs in the study.

B. European Clinical Study CLIN1901

In a prospective, interventional, multicenter study conducted in France, 61 subjects received treatment with EVOLYSSE™ SMOOTH to correct NLFs and perioral lines. After treatment, subjects recorded injection site reactions (ISRs) for 30 days. The intensity of ISRs after treatment with EVOLYSSE™ SMOOTH in the NLFs and perioral lines is shown in Table ***3***. Most ISRs were slight or moderate in intensity and resolved within the 30-day diary period.

Table 3: Injection Site Reactions by Maximum Intensity After Treatment with EVOLYSSE™ SMOOTH (N = 61)

ISR – NLFs	**Total % (n)**	**Slight % (n)**	**Moderate % (n)**	**Severe % (n)**
Swelling - Edema	47.5%(29)	29.5% (18)	14.8% (9)	3.3% (2)
Ecchymosis - Bruising	47.5% (29)	23.0% (14)	19.7% (12)	4.9% (3)
Induration - Firmness	41.0% (25)	31.1% (19)	8.2% (5)	1.6% (1)
Lumps/Bumps - Irregularity	39.3% (24)	21.3% (13)	16.4% (10)	1.6% (1)
Pain - Tenderness	27.9% (17)	21.3% (13)	4.9% (3)	1.6% (1)
Redness	24.6% (15)	18.0% (11)	6.6% (4)	0
Itching - Pruritus	9.8% (6)	9.8% (6)	0	0
Discoloration	6.6% (4)	6.6% (4)	0	0
ISR – Perioral Lines	**Total % (n)**	**Slight % (n)**	**Moderate % (n)**	**Severe % (n)**
Swelling - Edema	60.7% (37)	31.1% (19)	23.0% (14)	6.6% (4)
Ecchymosis - Bruising	45.9% (28)	18.0% (11)	21.3% (13)	6.6% (4)
Induration - Firmness	44.3% (27)	24.6% (15)	18.0% (11)	1.6% (1)
Lumps/Bumps - Irregularity	34.4% (21)	16.4% (10)	14.8% (9)	3.3% (2)
Pain - Tenderness	50.8% (31)	36.1% (22)	11.5% (7)	3.3% (2)
Redness	27.9% (17)	19.7% (12)	6.6% (4)	1.6% (1)
Itching - Pruritus	8.2% (5)	8.2% (5)	0	0
Discoloration	11.5% (7)	9.8% (6)	1.6% (1)	0

Of the 61 subjects treated with EVOLYSSE™ SMOOTH, 2 subjects (3.3%) had 3 treatment-related AEs, which included headache and induration. These AEs were all slight (mild) in intensity and resolved without sequelae.

7. CLINICAL STUDY

A. US Pivotal Study CLIN2101 for Facial Wrinkles and Folds

A multicenter, double blind, randomized, split face, controlled clinical trial was conducted to evaluate the safety and effectiveness of EVOLYSSE™ SMOOTH versus a control treatment for the correction of NLFs. A total of 70 subjects were randomized and treated with EVOLYSSE™ SMOOTH in one NLF and the control in the contralateral NLF. Optional touch-up treatments were administered two weeks after initial treatment. Routine follow-up visits for safety and effectiveness were conducted at 6 weeks, 3, 6, 9, and 12 months after initial treatment.

All subjects were offered an optional retreatment with EVOLYSSE™ SMOOTH for both NLFs at 12 months and a retreatment touch-up 2 weeks later, if needed, with the final study visit occurring 3 months after retreatment.

Study Endpoints

The primary effectiveness endpoint was a non-inferiority analysis of EVOLYSSE™ SMOOTH versus a control treatment at 6 months based on the validated 5-point Wrinkle Severity Rating Scale (WSRS) scores assigned to photos by an independent photo review (IPR) panel. The primary endpoint used the WSRS in the way in which it was validated (i.e., photo assessments).

Secondary effectiveness endpoints included:

- WSRS responder rates (defined as the percentage of subjects with at least a 1-point improvement since baseline) based on the IPR and blinded live evaluator assessments
- Global Aesthetic Improvement Scale (GAIS) responder rates (defined as subjects rated as improved, much improved, or very much improved compared to baseline) based on blinded live evaluator and subject assessments
- Subject satisfaction based on the validated FACE-Q Appraisal of Nasolabial folds questionnaire

Subject Demographics

Subject demographics and pretreatment characteristics are presented in Table 4 below.

Table 4: Subject Demographics and Pretreatment Characteristics

Demographic/Characteristic	N = 70
Age (years)	
Mean	57.3
Min, Max	31 – 84
Gender	
Female	57 (92.9%)
Male	5 (7.1%)
Race	
White	50 (71.4%)
Black/African American	19 (27.1%)
Other	0
Asian	0
Multiple	1 (1.4%)

Demographic/Characteristic	N = 70
Ethnicity	
Hispanic or Latino	18 (25.7%)
Not Hispanic or Latino	52 (74.3%)
Fitzpatrick Skin Type	
I	1 (1.4%)
II	16 (22.9%)
III	22 (31.4%)
IV	14 (20.0%)
V	11 (15.7%)
VI	6 (8.6%)
Median Baseline WSRS Score	
EVOLYSSE™ SMOOTH	3
Control	3

Effectiveness Results

The primary endpoint was met. Based on the IPR results using the WSRS, the difference in change from baseline was in favor of EVOLYSSE™ SMOOTH versus control at 6 months, -0.2 (95% CI [-0.416, -0.019]), and the upper confidence interval did not cross the non-inferiority margin of a 0.5 grade change. The corresponding p-value was < 0.001. The IPR responder rates at 6 months for Evolysse™ SMOOTH and control are shown in Table 5.

Table 5: WSRS IPR Responder Rates at Month 6

Evolysse™ SMOOTH	Control
51.6% (32/62)	35.5% (22/62)

Throughout the 12-month follow-up period (Table 6) EVOLYSSE™ SMOOTH continued to provide a clinically significant improvement in wrinkle severity with most NLFs maintaining improvement through 12 months [64.6% (42/65)] based on BLE assessments.

At Month 6, the GAIS responder rate was 98.4% (61/62) based on BLE assessments and 95.2% (59/62) based on the subject assessments. At 1 year, the BLE GAIS responder rate was 64.6% (43/65) and the subject GAIS responder rate was 92.3% (60/65).

Table 6: Effectiveness Results through 1 Year (mITT)

Visit	BLE WSRS Responder Rate % (n/N)	GAIS Responder Rate % (n/N)	
		BLE	Subject
Month 3	92.3% (60/65)	95.4% (62/65)	96.9% (63/65)
Month 6	93.5% (58/62)	98.4% (61/62)	95.2% (59/62)
Month 9	80.3% (49/61)	88.5% (54/61)	83.6% (51/61)
Month 12	64.6% (42/65)	66.2% (43/65)	92.3% (60/65)

The mean score on the Appraisal of Nasolabial Folds module of the FACE-Q questionnaire for the EVOLYSSE™ SMOOTH group improved from 34.1 at baseline to 65.3 at 6 months and 56.6 at 12 months. These improved scores indicate that subjects were satisfied with the appearance of their NLFs after treatment with EVOLYSSE™ SMOOTH compared to baseline.

B. European Clinical Study CLIN1901

EVOLYSSE™ SMOOTH was evaluated for the correction of facial wrinkles and folds in a prospective, interventional, multicenter study conducted in France. A total of 61 subjects received treatment in the NLFs and perioral lines with follow-up through 12 months.

The Investigators assessed wrinkle severity of the NLFs and perioral lines using the 6-point Lemperle Rating Scale (LRS). Most subjects showed a clinically significant improvement (i.e., ≥ 1-point improvement) in wrinkle severity through 12 months after treatment with EVOLYSSE™ SMOOTH (Table 7).

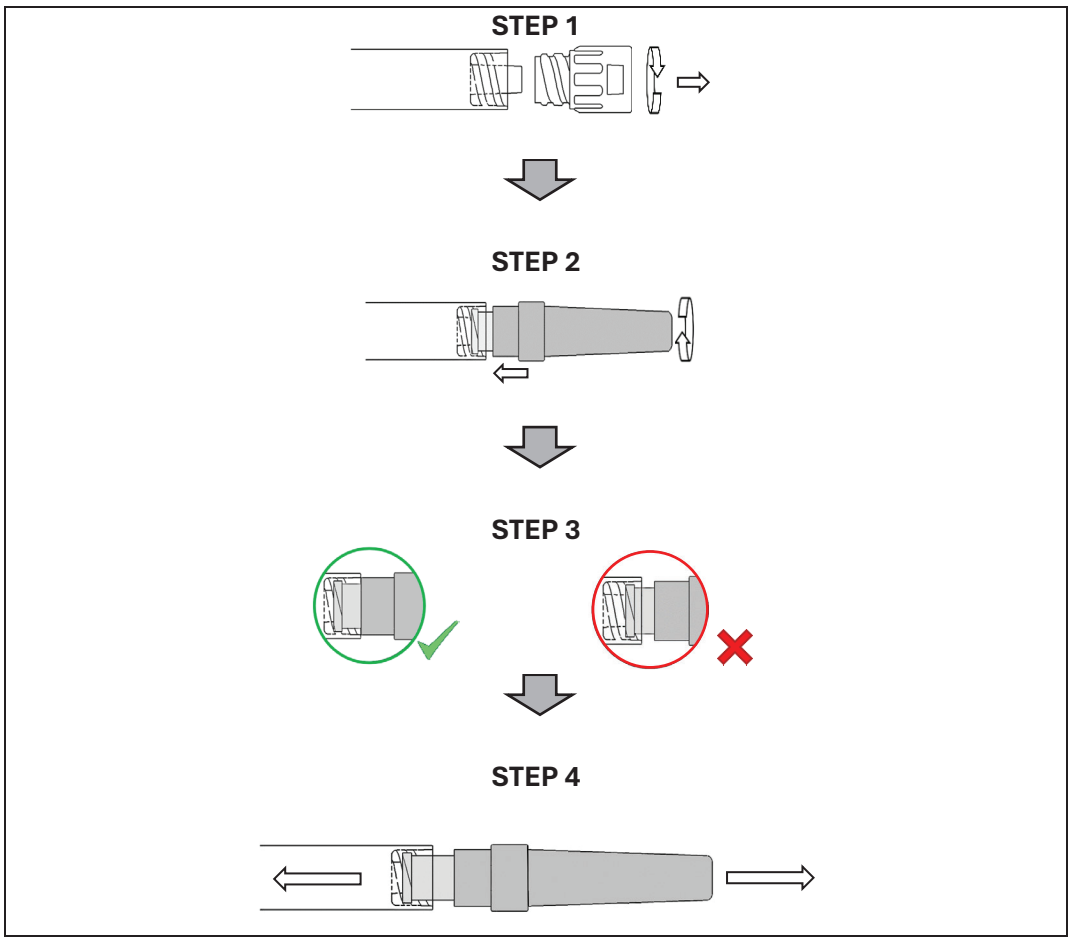
Table 7: Investigator LRS Responder Rates (N = 61)

Timepoint	NLF Responder Rate % (n)	Perioral Lines Responder Rate % (n)
Day 30	98.4% (60)	93.4% (57)
Month 3	83.6% (51)	91.8% (56)
Month 6	77.0% (47)	86.9% (53)
Month 9	65.0% (39)	81.7% (49)
Month 12	54.1% (33)	73.8% (45)

8. INSTRUCTIONS FOR USE

1. Prior to treatment, the subject's medical history should be obtained, and the subject should be fully apprised of the indications, contraindications, warnings, precautions, potential outcomes, adverse events, and method of administration.
2. Use the needles supplied with the syringe.
3. Attach the needle to the syringe, as shown in Figure 1, and according to the following instructions. Only the needles provided with EVOLYSSE™ SMOOTH should be used for injection.
   - Use medical gloves.
   - Carefully remove the stopper from the syringe (step 1).
   - Insert the hub of the needle into the syringe body and turn it clockwise (step 2).
   - Firmly screw the needle onto the tip of the syringe, holding it by its shield. Continue to tighten the needle until it is seated in the proper position (step 3). If the needle is not properly screwed into position, it may disconnect or result in leakage of the gel.
   - Remove the shield just before injection and after skin disinfection (step 4).

Figure 1: Attachment of the Needle to the Syringe



4. Cleanse the area to be treated with a suitable antiseptic solution (without quaternary ammonium compounds).
5. To avoid breakage of the needle, do not attempt to bend or manipulate it before or during injection.
6. Before injecting the gel, press the plunger rod slowly until a small droplet is visible at the tip of the needle.

Injection Technique

1. EVOLYSSE™ SMOOTH is injected into the dermis and/or subdermis using the supplied 30G ½" needles for versatility in treating dynamic wrinkles and folds.
2. Aspiration is recommended prior to implantation to avoid inadvertent injection into a blood vessel.
3. The injection technique may vary in angle and orientation of the needle bevel, injection depth, and quantity administered. The injection techniques used in the pivotal clinical study included retrograde and antegrade linear threading, crosshatching, and serial puncture to achieve optimal results.
4. Inject the gel slowly by gently pressing down on the plunger rod. If the needle is obstructed, do not increase the pressure with the tip of the plunger. Stop the injection and use a new needle.

5. Inject to the desired volume effect for optimal correction. Do not overcorrect. In the pivotal clinical study, the average injection volume to achieve optimal outcomes was 1.0 mL per NLF (range 0.4-1.9 mL). The mean injection volume per NLF was 0.7 mL at initial treatment, 0.4 at touch-up treatment, and 0.6 mL at retreatment.
6. If immediate blanching occurs, the injection should be stopped, and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.
7. After injecting the gel, the treated area may be gently massaged.
8. The syringe and needles must be discarded immediately after use in accordance with accepted medical practice and applicable local, state, and federal requirements.

9. HOW SUPPLIED

The gel is supplied sterile in a 1 mL plastic syringe assembled with a plunger rod and finger rest. Sterile 30G ½" ultra-thin wall needles are provided for injection. EVOLYSSE™ SMOOTH and the needles are for single use only.

10. STORAGE

Store at room temperature (up to 25°C/77°F). Protect from sunlight. Do not freeze.

11. SHELF-LIFE

The expiration date of the device is printed on the label. Do not use after the expiration date.

12. SYMBOLS



Catalog Number



Unique Device Identifier



Lot/Batch Number


Expiration Date (YYYY-MM-DD)



Steam Sterilized

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