RADIESSE®
INJECTABLE IMPLANT

MERZ AESTHETICS®

INSTRUCTIONS FOR USE

1 DESCRIPTION

RADIESSE® Injectable Implant is a steam sterilized, latex-free, non-pyrogenic, semi-solid, cohesive, completely bio-degradable sub-dermal implant. The principal component is synthetic calcium hydroxylapatite, a biomaterial with over twenty years of use in orthopedics, neurosurgery, dentistry, otolaryngology and ophthalmology. Calcium hydroxylapatite is the primary mineral constituent of bone and teeth. The semi-solid nature of the implant is created by suspending calcium hydroxylapatite in a gel carrier that consists primarily of water (sterile water for injection USP) and glycerin (USP). The gel structure is formed by the addition of a small amount of sodium carboxymethylcellulose (USP). The gel is dissipated *in vivo* and replaced with soft tissue growth, while the calcium hydroxylapatite remains at the site of injection. The result is long-term yet non-permanent restoration and augmentation.

RADIESSE® Injectable Implant 1.5 mL has a particle size range of 25-45 microns and can be injected with a 27 gauge inner diameter (ID) or larger diameter needle with a standard Luer fitting.

Use of needles with inner diameters smaller than 27 gauge may increase the incidence of needle occlusion.

2 INTENDED USE / INDICATIONS

RADIESSE® Injectable Implant is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus, and for the rejuvenation of the hand. RADIESSE® Injectable Implant diluted 1:2 with 0.9% sterile saline for injections is intended for the treatment of moderate and severe décolleté wrinkles.

3 CONTRAINDICATIONS

- RADIESSE® Injectable Implant is contraindicated in the presence of acute and/or chronic inflammation or infection when these involve the area to be treated.
- RADIESSE® Injectable Implant is contraindicated in patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- RADIESSE® Injectable Implant is not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® Injectable Implant is contraindicated in patients prone to developing inflammatory skin conditions.
- RADIESSE® Injectable Implant is contraindicated in areas with pre-existing dermal compromise, including but not limited to scars (with a history of hypertrophic scarring or keloids), tattoos and piercings.
- Do not implant in the epidermis or use as a skin replacement. Implantation into the epidermis or superficial dermis could lead to complications such as fistula formation, infections, extrusions, nodule formation and induration.
- Not intended to be used for the correction of glabellar folds and nose area. A higher incidence of localized necrosis has been associated with glabellar and nose injection. Complications indicate that forceful injection into superficial dermal vessels of the glabellar or nose area could cause retrograde movement into the retinal arteries resulting in vascular occlusion.
- RADIESSE® Injectable Implant is contraindicated in the presence of foreign bodies such as liquid silicone or other particulate materials.
- RADIESSE® Injectable Implant should not be used in areas where there is inadequate coverage of healthy, well vascularized tissue.
- RADIESSE® Injectable Implant should not be used in patients with systemic disorders which cause poor wound healing or will lead to tissue deterioration over the implant.

- RADIESSE® Injectable Implant is contraindicated in patients with bleeding disorders.
- Not intended for use in the breasts or nipples.
- Not intended for use in the lips.
- Contraindicated in patients with tendency for hyperpigmentation.
- Contraindicated in persons under 18 years.
- Contraindicated during pregnancy and in breastfeeding females.

4 WARNINGS

- Introduction of RADIESSE® Injectable Implant into the vasculature may lead to embolization or thrombosis, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example inject the RADIESSE® Injectable Implant slowly and apply the least amount of pressure necessary.
- Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures.
- Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure.
- Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur.
- RADIESSE® Injectable Implant should not be injected into organs or other structures that could be damaged by a space occupying implant.
- Do not overcorrect (overfill) the injection site as the soft tissue volume is expected to increase within several weeks as the treatment effect of RADIESSE® Injectable Implant occurs.
- RADIESSE® Injectable Implant should not be implanted in patients while the patient is on an aspirin regimen or while taking other medications that could inhibit the healing process.
- RADIESSE® Injectable Implant should not be implanted in infected or potentially infected tissue or in open cavities because infection or extrusion may occur. A significant infection may result in damage or loss to the skin overlying the implant. Hematomas or seromas may require surgical drainage.
- Use of RADIESSE® Injectable Implant in patients with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- In the event of a hypersensitivity or allergic reaction, a significant inflammation or infection may occur requiring the removal of the implant.
- Some injectable implants have been associated with hardening of the tissues at an injection site, migration of particles from an injection site to other parts of the body and/or allergic or autoimmune reactions.
- As with any implant material, possible adverse reactions which may occur include, but are not limited to, the following: inflammation, infection, fistula formation, extrusion, hematoma, seroma, induration formation, inadequate healing, skin discoloration and inadequate or excessive augmentation.

4.1 SPECIFIC WARNINGS RELATED TO INJECTIONS INTO HANDS

- Special care should be taken to avoid injection into veins or tendons in the hand. Injection into tendons may weaken tendons and cause tendon rupture. Injection into veins may cause embolization or thrombosis.
- Injection into the hand may cause side effects/adverse events that last for more than 14 days. Refer to Section “Side Effects and Adverse Events” for details.
- Injection in the dorsum of the hand may result in temporary difficulty performing activities (48% of study persons reported this adverse event). Fitzpatrick Skin Types IV-VI may have an increased risk in difficulty performing activities (68% of Fitzpatrick Skin Types IV-VI reported this event).
- RADIESSE® Injectable Implant may cause nodules, bumps, or lumps in the dorsum of the hand (12% reported this event) and can last up to one year.
- Injection into persons with very severe loss of fatty tissue with marked visibility of veins and tendons has not been studied. The safety and effectiveness in this population has not been established.

- Possible acute carpal tunnel syndrome or exacerbation of pre-existing compressive median neuropathy in the wrist may occur. Volumes over 3 mL of RADIESSE® Injectable Implant per hand in a treatment session have not been studied. Increased bruising is associated with higher volume injection. Re-treatment with RADIESSE® Injectable Implant of volumes greater than approximately 1.6 mL per hand in a treatment session can result in increased side effects/adverse events (redness, pain, swelling, and difficulty performing activities).

4.2 SPECIFIC WARNINGS RELATED TO INJECTIONS IN THE DECOLLETÉ AREA

- RADIESSE® Injectable Implant diluted 1:2 with 0.9% sterile saline should be injected in the subdermal plane sufficiently deep to prevent nodular formation at the surface of the skin or ischemia of the overlying tissue or discoloration of the skin.

5 PRECAUTIONS

- In order to minimize the risks of potential complications, RADIESSE® Injectable Implant should only be used by health care practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
- In order to minimize the risks of potential complications, health care practitioners should fully familiarize themselves with the product, the product educational materials and the entire package insert.
- 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.
- As with all transcutaneous procedures, RADIESSE® Injectable Implant injection carries a risk of infection. Infection may necessitate attempted surgical removal of RADIESSE® Injectable Implant. Standard precautions associated with injectable materials should be followed.
- Persons who are using medications that can prolong bleeding, such as aspirin or warfarin, may, as with any injection, experience increased bruising or bleeding at the injection site.
- The calcium hydroxylapatite (CaHA) particles of RADIESSE® Injectable Implant are radiopaque and are clearly visible on CT and MRI scans or mammograms and may be visible in standard, plain radiography. Persons need to be informed of the radiopaque nature of RADIESSE® Injectable Implant, so that they can inform their primary care health care practitioners as well as radiologists. In a radiographic study of 58 persons, there was no indication of RADIESSE® Injectable Implant potentially masking abnormal tissues or being interpreted as tumors in CT scans.
- Patients with a port, pacemaker, or implanted defibrillator should be carefully evaluated before treatment with RADIESSE® Injectable Implant. The health care practitioners should assess the potential risk of device interference.
- RADIESSE® Injectable Implant requires soft tissue for easy percutaneous injection. Scar tissue and significantly compromised tissue may not accept the implant appropriately.
- Infection requiring treatment may occur at the injection site. If such infection cannot be corrected, it may become necessary to remove the implant.
- Injection related reactions, including bruising, erythema, swelling, pain, itching, discoloration or tenderness, may occur at the site of the injection. These usually resolve spontaneously within one to two days after the injection.
- Nodule(s) may form requiring treatment or removal.
- Contour irregularities of the implant may occur which may require a surgical procedure to correct.
- Do not over-inject the area to be treated. In extreme cases site rupture could occur. RADIESSE® Injectable Implant can be easily added in subsequent injections but cannot be easily removed.
- The RADIESSE® Injectable Implant injection procedure, like similar injection procedures, has small but inherent risks of infection and/or bleeding. The patient may experience slight discomfort during and following the procedure. Therefore, anesthetic techniques common with this treatment should be considered. The usual precautions associated with percutaneous injection procedures should be followed to prevent infection.
- **Do not re-sterilize.** RADIESSE® Injectable Implant is supplied sterile and non-pyrogenic in a sealed foil pouch and is intended for single patient, single treatment use only.
- The foil pouch should be carefully examined to verify that neither the pouch nor the syringe has been damaged during shipment. Do not use if the foil pouch is compromised or the syringe has been damaged. Do not use if the syringe end cap or syringe plunger is not in place. *There is a small amount of moisture normally present inside the foil pouch for sterilization purposes; this is not an indication of a defective product.*
- 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 re-shield used needles. Recapping by hand is a hazardous practice and should be avoided.
- The safety of RADIESSE® Injectable Implant with concomitant dermal therapies such as epilation, UV irradiation, radiofrequency, ablative or non-ablative laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- No studies of interactions of RADIESSE® Injectable Implant with drugs or other substances or implants have been conducted.
- Limited clinical data is available on the combination of RADIESSE® Injectable Implant with BELOTERO® products and/or botulinum toxin. As a precaution, products should be injected in different facial areas. Health care practitioners should be experienced, and persons appropriately selected as not only benefits, but also side effects/adverse events can be cumulative, and causality of side effects/adverse events could become difficult to determine. Instructions for use, depth of injection and appropriate recommendation of each product should be followed.
- Universal precautions must be observed when there is a potential for contact with a person´s body fluids. The injection session must be conducted with aseptic technique.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with RADIESSE® Injectable Implant, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if RADIESSE® Injectable Implant is administered before the skin has healed completely after such a procedure.
- Injection of RADIESSE® Injectable Implant into persons with a history of previous herpetic eruption may be associated with reactivation of the herpes virus.

5.1 SPECIFIC PRECAUTIONS RELATED TO INJECTIONS INTO HANDS

- Use of RADIESSE® Injectable Implant in the dorsum of the hand in persons with diseases, injuries or disabilities of the hand has not been studied. Care should be taken when treating persons with autoimmune disease affecting the hand, hand implants, Dupuytren's contracture, history of hand tumor, vascular malformations, Raynaud's disease, and persons at risk for tendon rupture.
- Use of RADIESSE® Injectable Implant in the dorsum of the hand may result in significant swelling of the dorsum of the hand. Persons should be instructed to remove jewelry (rings) before treatment and until swelling has resolved to avoid compromise of finger circulation.
- The effects of RADIESSE® Injectable Implant injection on hand function are uncertain.
- Safety of RADIESSE® Injectable Implant injected into the dorsum of the hand in persons under 26 years old and over 79 years old has not been studied.
- Safety of RADIESSE® Injectable Implant beyond one year in the hand has not been investigated in clinical trials.

6 INDIVIDUALIZATION OF TREATMENT

Before treatment, the patient's suitability for the treatment and the patient's need for pain relief should be assessed. The outcome of treatment will vary among patients. In some instances, additional treatments may be necessary depending on the size of the defect and the needs of the patient. Additional injections may be performed, but only after sufficient time has passed to evaluate the patient. The patient should not be re-injected sooner than seven days after the previous treatment.

7 INCIDENT REPORTING

Any incident that directly or indirectly led, might have led or might lead to any of the following: the death of a patient, user or other person, the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, or a serious public health threat; and that has occurred in relation to the device should be reported under AxCA-adverse.events@merz.com or 1-877-336-4008 (Customer Service).

In case of serious incident, please contact in addition Ax-Safety@merz.de

For Quality complaints please contact AxCA-QA@merz.com or 1-877-336-4008 (Customer Service).

8 SIDE EFFECTS AND ADVERSE EVENTS

The following side effects/adverse events have been identified during the use of RADIESSE® Injectable Implant. Because they are reported voluntarily from a population (including from literature) of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to RADIESSE® Injectable Implant. These events have been chosen for inclusion due to the combination of their seriousness, frequency of reporting, or potential causal connection to RADIESSE® Injectable Implant:

infection (incl. biofilm formation), cellulitis, impetigo, loss of effect, product displacement/migration, allergic reaction, anaphylaxis (incl. dyspnoea), hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, nodules, induration, erythema, skin discoloration (including hypo- and hyperpigmentation), dissatisfaction, papule/pustule, skin pallor, hair loss, paresthesia, hypoesthesia, ptosis, pain (incl. mastication pain, arthralgia, myalgia), headache, swelling/edema, tightness, asymmetry, abscess, herpetic infection including herpes simplex and herpes zoster, hematoma, petechiae/purpura, injection site hemorrhage, blanching, blistering, scab, abrasion, dizziness, festoons, flu-like symptoms, fever, malaise, asthenia, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, lymphatic obstruction, nausea, vomiting, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, vascular injury, ocular ischemia, diplopia, visual impairment/blindness, optic nerve injury, papilloedema, retinal disorder, facial muscle paralysis, Bell's palsy, syncope, chewing problems, injection site erosion, injection site cyst, injection site deformation, injection site dysaesthesia, injection site telangiectasia, injection site vesicles, injection site warmth, aggravation of preexisting conditions, superficial vein prominence, vasculitis, nerve injury, nerve compression, xanthelasma, skin photosensitivity reaction.

Persons with specific ethnic characteristics, e.g., Asian population, should be informed of a higher risk of tissue reactions, e.g., inflammatory reactions, pigmentary disorders, post-inflammatory hyperpigmentation (PIH), scarring, and keloid formation upon cutaneous injury.

The following interventions have been reported: antibiotics, anti-inflammatories, corticosteroids, antihistamines, analgesics, massage, warm compress, excision, drainage, and surgery. This information does not constitute and is not intended to be medical advice, a recommendation on how to treat a side effect/adverse event or an exhaustive list of possible interventions. Health care practitioners should evaluate each case on an individual basis, and independently determine, based on their professional experience, what treatment(s) are appropriate, if any, for their patients.

9 DIRECTIONS FOR USE

9.1 DEVICE PRESENTATION

RADIESSE® Injectable Implant is provided sterile and non-pyrogenic in a syringe packaged in a foil pouch and boxed for convenient storage.

Each syringe unit with needle convenience pack consists of one pre-filled syringe containing 1.5 mL of RADIESSE® Injectable Implant and two Terumo K-Pack II 27G thin wall injection needle(s). The degree of accuracy of syringe graduations is ±0.025 mL.

The needles by Terumo provided within the carton package of RADIESSE® Injectable Implant are sterilized by ethylene oxide. Needles are intended for single-use as well.

9.2 SINGLE USE

Do not use if packaging and/or syringe are damaged or if the syringe end cap or syringe plunger is not intact.

The contents of the syringe are intended for single person, single treatment use only and cannot be re-sterilized. Re-use may compromise the functional properties of the device and/or lead to device failure. Re-use may also create a risk of contamination of the device and/or cause person infection or cross-infection including but not limited to transmission of infectious disease(s) and blood transfer between persons. All which, in turn, may lead to person injury, illness or death.

9.3 PREPARATIONS, POSOLOGY AND ADMINISTRATION METHOD

9.3.1 Preparation of RADIESSE® Injectable Implant for Face and Hand Treatment

The following is required for the percutaneous injection procedure:

- One RADIESSE® Injectable Implant syringe 1.5 mL.
- Appropriate size needle(s) with Luer lock fittings. The preferred size is a 27G or larger needle with a standard Luer fitting. Use of needles smaller in diameter than 27G may increase the incidence of needle occlusion.

1. Prepare patient for percutaneous injection using standard methods. The treatment injection site should be marked by a surgical marker and prepared with a suitable antiseptic. Local or topical anesthesia at the injection site or sedation should be used at the discretion of the health care practitioner. After anesthetizing the site, apply ice to the area to decrease local swelling/distention.
2. Prepare the syringes and the injection needle(s) before the percutaneous injection. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe for same patient treatment.

   Remove foil pouch from the carton. The pouch can be opened, and the syringe dropped onto the sterile field when required. *There is a small amount of moisture normally present inside the foil pouch for sterilization purposes; this is not an indication of a defective product.*

   Peel or twist apart the needle packaging to expose the hub. For use of needles other than the needle(s) provided with this package, follow the directions provided with the needle(s).

   Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle. The syringe can then be twisted onto the Luer lock fitting of the needle, taking care not to contaminate the needle when removing its protective cap. **The needle must be tightened securely to the syringe and primed with RADIESSE® Injectable Implant.** If excess implant is on the surface of the Luer lock fittings, it will need to be wiped clean with sterile gauze. Slowly push the syringe plunger until the implant material extrudes from the end of the needle. If leakage is noted at the Luer fitting, it may be necessary to tighten the needle or to remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle.
3. Locate the initial site for the implant. Scar tissue and cartilage may be difficult or impossible to inject. Avoid passing through these tissue types when advancing the injection needle.

9.3.2 Technique for Mixing RADIESSE® Injectable Implant and 2% Lidocaine HCl

CAUTION: Do not use the RADIESSE® Injectable Implant and 2% lidocaine mixture for décolleté treatment. The mixing procedure for décolleté treatment is described in section 9.3.4. below.

CAUTION: Do not use the RADIESSE® Injectable Implant and 2% lidocaine mixture later than 2 hours after mixing.

CAUTION: The assembled components are intended for one-time use only.

1. Assemble the components and perform the mixing using sterile technique (see Figure 1).

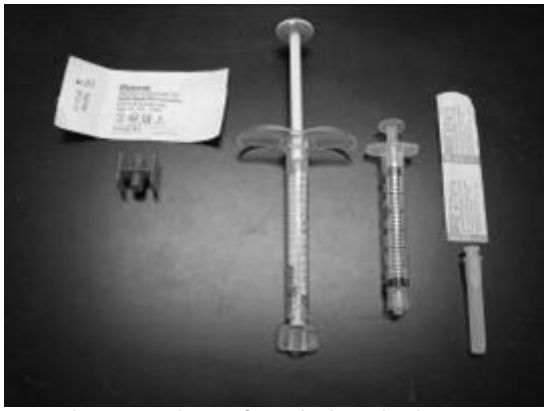


Figure 1: Left to right: Female-to-female luer lock connector, RADIESSE® syringe, 3.0 mL mixing syringe, sterile 27 gauge, 0.5" needle

2. Draw the lidocaine into a 3.0 mL sterile polypropylene mixing syringe fitted with a sterile 27 gauge, 0.5" needle.
3. Tap the mixing syringe, containing lidocaine and depress its push rod to remove all excess air.

4. Remove the sterile 27 gauge, 0.5” needle.
5. Firmly connect the mixing syringe to the RADIESSE® syringe using the female-to-female luer lock connector (see Figures 2 and 3).

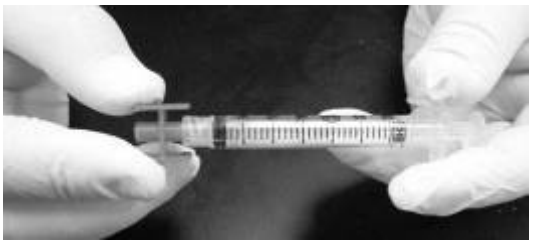


Figure 2

Figure 3

6. Mix the lidocaine and RADIESSE® Injectable Implant by alternately depressing the plungers, first on the mixing syringe and then on the RADIESSE® syringe for ten mixing strokes (each mixing stroke is one complete compression of the mixing syringe plunger followed by one complete compression of the RADIESSE® syringe plunger). Plungers are compressed firmly and quickly, at about two compressions per second.

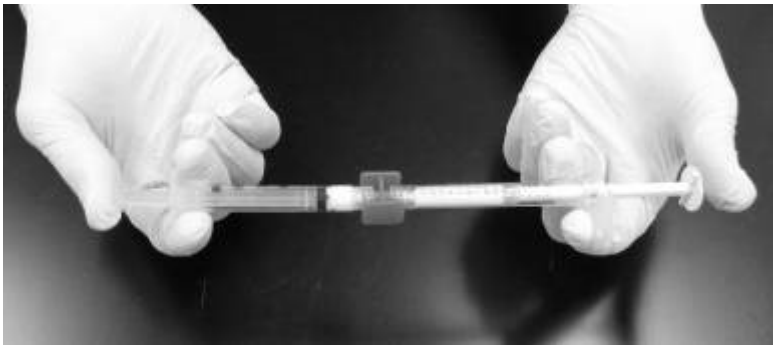


Figure 4

7. After mixing, remove the mixing syringe and the female-to-female luer lock connector and discard.
8. Fit the syringe containing the lidocaine and RADIESSE® mixture with an injection needle.
9. Proceed with the injection of the RADIESSE® Injectable Implant.

The table below provides the ratio of 2% lidocaine to be mixed with the various syringe volumes of RADIESSE® Injectable Implant.

These ratios result in a 0.3% concentration of 2% lidocaine (w/v%).

LIDOCAINE CONCENTRATION

RADIESSE® (mL)	2% Lidocaine (mL)	Resulting Lidocaine Concentration (w/v%)
1.5	0.26	0.31% - 0.32%

9.3.3 Posology and Administration Method of RADIESSE® Injectable Implant for Face and Hand treatment

GENERAL

NOTE: Do not inject into a blood vessel.

- The depth of the injection and the amount injected will vary depending on the site and extent of the restoration or augmentation. RADIESSE® Injectable Implant should be injected in the subdermis so as to prevent nodular formation at the surface of the skin or ischemia of the overlying tissue. For hand rejuvenation, Injectable Implant should be injected in the areolar plane between the subcutaneous layer and superficial fascia.

- **DO NOT OVERCORRECT THE INJECTION SITE.** Use a 1:1 correction factor. Mold or massage the injected implant periodically during the injection process to maintain a smooth contour of the implant.
- Inject the product slowly and apply the least amount of pressure necessary.
- A maximum of 10 mL RADIESSE® Injectable Implant is recommended as yearly dose for facial indications and hands. The dose may be adapted or increased according to the person's indication(s), tissue, age, injection depth and technique for implantation.
- If significant resistance is encountered when pushing the plunger, the injection needle may be moved slightly to allow easier placement of the material. If significant resistance is still encountered, it may be necessary to pull the needle entirely out of the injection site and try again in a new position. If significant resistance continues to persist, it may be necessary to try a different injection needle. If this is not successful, replace the syringe and injection needle.
- Advance the needle bevel down at approximately a 30° angle to the skin into the sub-dermis to the starting location. [Refer to additional instructions, below, for augmentation of specific facial areas.] Carefully push the plunger of the syringe to start the injection and slowly inject the implant material while withdrawing the needle, placing a line of material in the desired location. Continue placing additional lines of material until the desired level of augmentation is achieved. The thread of implant material should be completely surrounded by soft tissue without leaving globular deposits.
- For hand rejuvenation, DO NOT inject RADIESSE® Injectable Implant in linear threads. Inject in a bolus form between the central tendons in the dorsum of the hand and distribute the material through massage.

AUGMENTATION OF CHEEKS, FACE OR CORNER OF THE MOUTH

1. Insert needle with bevel down at approximately a 30° angle to the skin. The needle should slide into the deep dermis to the point you wish to begin the injection. This should be easily palpable with the non-dominant hand.
2. Apply slow continuous even pressure to the syringe plunger to inject the implant as you withdraw the needle, leaving behind a single thin thread or strand of implant material. The thread of implant material should be completely surrounded by soft tissue without leaving globular deposits.
3. Individual threads of implant material should be placed parallel and adjacent to each other and layered when deeper folds are corrected. As an option, the threads can be cross layered in a deeper plane for structural support.
4. After injection, use the index finger and thumb to smooth the areas and better distribute the implant in case of any slight nodular deposition of material.
5. Injection can be made in the subcutaneous tissue or muscle, but not adjacent to bone or in the epidermis.
6. Injection treatments in the same anatomical location must be spaced by at least 4 weeks.

Injection Procedure for Hand Treatment

- Prepare person for percutaneous injection using standard methods. Have the person wash both hands with soapy water producing friction for 5-10 minutes and then prepare hands with suitable antiseptic. The treatment injection site may be marked for planned injection sites. Jewelry should be removed prior to injection and until post-procedure swelling has resolved.
- Using the syringe of RADIESSE® Injectable Implant fitted with the injection needle, slowly push the syringe plunger until RADIESSE® Injectable Implant extrudes from the end of the needle. Perform aspiration before bolus injection to avoid intravascular injection. If leakage is noted at the Luer fitting, wipe it clean with sterile gauze. It may be necessary to tighten the needle, remove the needle and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle. A new injection needle may be used for each syringe, or the same injection needle may be connected to each new syringe for same person treatment.
- Locate the initial site for injection. Persons are to receive injections in the dorsum of the hands between the 1st and 5th metacarpals. Injection should initially occur between the 2nd and 4th metacarpals, taking care not to inject close to the metacarpophalangeal joints. If necessary to achieve optimal correction, injection is also allowed between the 1st and 2nd and 4th and 5th metacarpals.
- Skin tenting should be performed to separate the skin from vascular and tendinous structures by using the thumb and forefinger of the non-injecting hand to lift skin over the dorsal aspect of the hand being treated.

- Advance the needle between the subcutaneous layer and superficial fascia with the syringe parallel to the dorsum of the hand. Carefully push the plunger of the RADIESSE® Injectable Implant syringe to start the injection and inject the RADIESSE® Injectable Implant material in small boluses, 0.2 – 0.5 mL/bolus. No more than 0.5 mL should be injected per bolus. The number of boluses will vary depending on the extent of treatment desired. No more than 3 mL of RADIESSE® Injectable Implant (two 1.5 mL syringes) will be injected per hand.
- If significant resistance is encountered when pushing the plunger, the injection needle may be moved slightly to allow easier placement of the material, or it may be necessary to change the injection needle.
- Immediately after injection, cover the injection site with a sterile 4x4 gauze and have person sit on this hand while the contralateral hand is being injected. This warms the RADIESSE® Injectable Implant making it more malleable for later massaging.
- Treat the contralateral hand in the same manner as described in the steps above.
- Immediately after injection of the contralateral hand, cover the injection site with a sterile 4x4 gauze and have the person sit on this hand.
- While the contralateral hand is warming, remove the gauze from the hand that was initially injected, have the person make a fist with this hand, and gently massage the dorsum of the hand until RADIESSE® Injectable Implant has been evenly spread across the dorsum remaining distal to the wrist crease and proximal to the metacarpophalangeal joints.
- Use a 1:1 correction factor. No overcorrection is needed.
- Injection treatments in the same anatomical location of hands must be spaced by at least 6 months.

9.3.4 Preparation of RADIESSE® Injectable Implant diluted with saline 1:2 for the Treatment of the Décolleté

Only one (1) RADIESSE® Injectable Implant syringe 1.5 mL is used for the preparation of RADIESSE® Injectable Implant diluted with saline 1:2.

The injection of RADIESSE® Injectable Implant diluted with saline 1:2 for décolleté treatment needs to be done within 30 minutes after dilution.

The following needle is recommended for injection:

Description	Qty.
Injection needles (27G x 3/4”)	3

Use of needles smaller in diameter than 27G may increase the incidence of needle occlusion.

The following cannula is recommended for injection:

Description	Qty.
Cannula, blunt tip, 25G x 2” (0.5 x 50 mm)	3
Needle Guide, 23 G x ¾” (0.60 x 19 mm; for pre-hole)	3

For décolleté treatment RADIESSE® Injectable Implant is diluted with sterile physiological saline solution (0.9% NaCl) for injections. Dilution of RADIESSE® Injectable Implant is to be performed with the following auxiliary components:

Description	Manufacturer	Qty.	Article number
RADIESSE® Injectable Implant 1.5 mL	Merz North America, Inc.	1	8071
RAPIDFILL Connector Luer Lock to Luer Lock	Baxter Healthcare Corporation	1	13901
BD Luer-Lock Tip Syringe (5 mL)	Becton, Dickinson and Company	2	309646

Blunt needle (18G x 1½”)	At the discretion of the Health Care Practitioner	1	N/A
Sterile physiological saline solution (0.9% NaCl)	At the discretion of the Health Care Practitioner	3.0 mL	N/A

Dilution Table

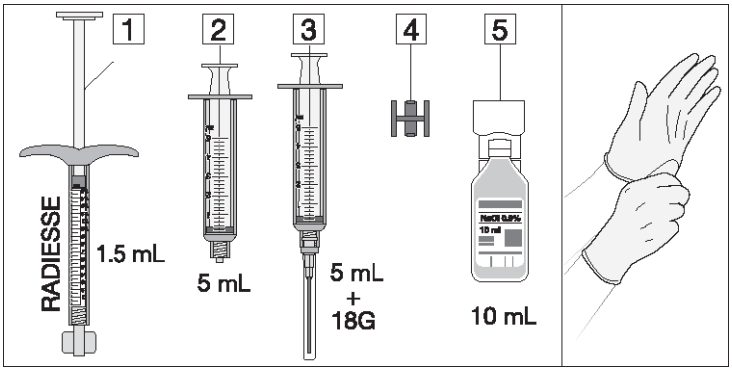
The following table shows the ratio of RADIESSE® Injectable Implant and saline for the preparation of RADIESSE® Injectable Implant diluted with saline 1:2.

Dilution factor	**Amount of RADIESSE® Injectable Implant (mL)**	**Amount of saline (mL)**	**Total volume of the implant (mL)**
1:2	1.5	3.0	4.5

Dilution Protocol

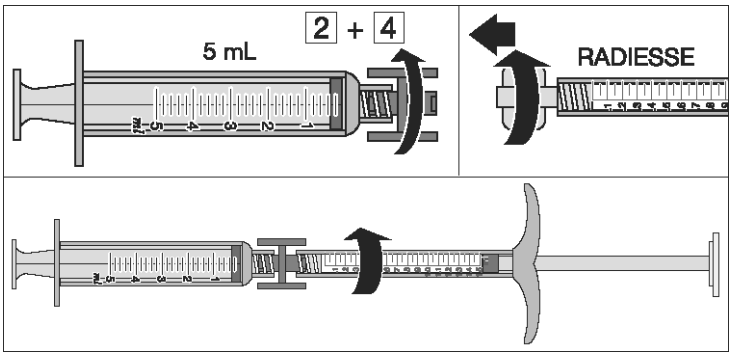
- **CAUTION:** Only use RADIESSE® Injectable Implant diluted with saline 1:2 within 30 minutes after preparation.
- **CAUTION:** The procedure has to be performed in an ambulatory setting under aseptic conditions. The person’s skin should be healthy and not inflamed. The skin should be rigorously cleaned with a topical antiseptic prior to any injection.
- **CAUTION:** The components used for preparation of RADIESSE® Injectable Implant diluted with saline 1:2 are intended for single-use only.
- **CAUTION:** Use only sterile 0.9% NaCl solution for injection to prepare RADIESSE® Injectable Implant diluted with saline 1:2.
- **CAUTION:** Check diluted RADIESSE® Injectable Implant for absence of foreign particles before use and discard the product, if foreign particles are visible.

A. Auxiliary components incl. solution



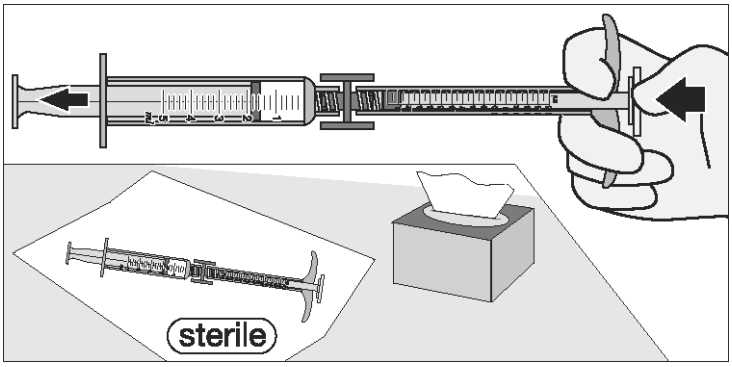
1. Provide sterile 0.9% saline solution for injection.
2. Select a RADIESSE® Injectable Implant and mixing components and check their expiry date.
3. Open the RADIESSE® Injectable Implant and mixing components and place the content on a clean and disinfected working surface.
4. **Wear gloves for the following procedure.**
5. Assemble the components and perform the dilution using aseptic technique.

B. Connect the Dilution Syringe and the RADIESSE® Injectable Implant Syringe



6. Firmly connect the RAPIDFILL Connector by screwing clockwise to a 5 mL BD Luer-Lock Syringe (Dilution syringe).
   There is no preferred direction for the Luer Connector.
7. Firmly connect the RADIESSE® Injectable Implant syringe to the opposite site of the RAPIDFILL Connector.

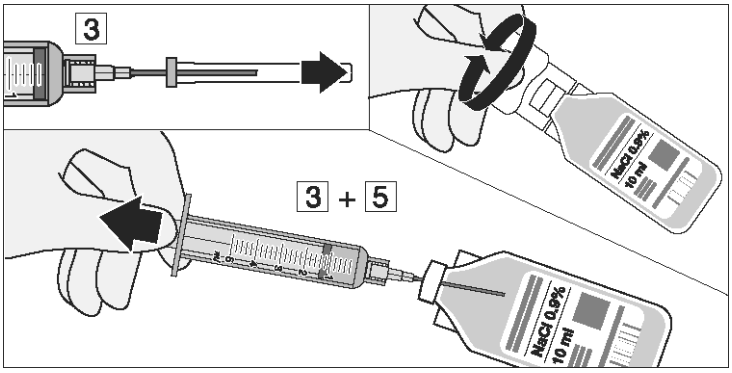
C. Transfer of RADIESSE® Injectable Implant



8. Transfer the entire RADIESSE® Injectable Implant into the dilution syringe.
9. Place the interconnected syringes on a cleaned and disinfected surface.

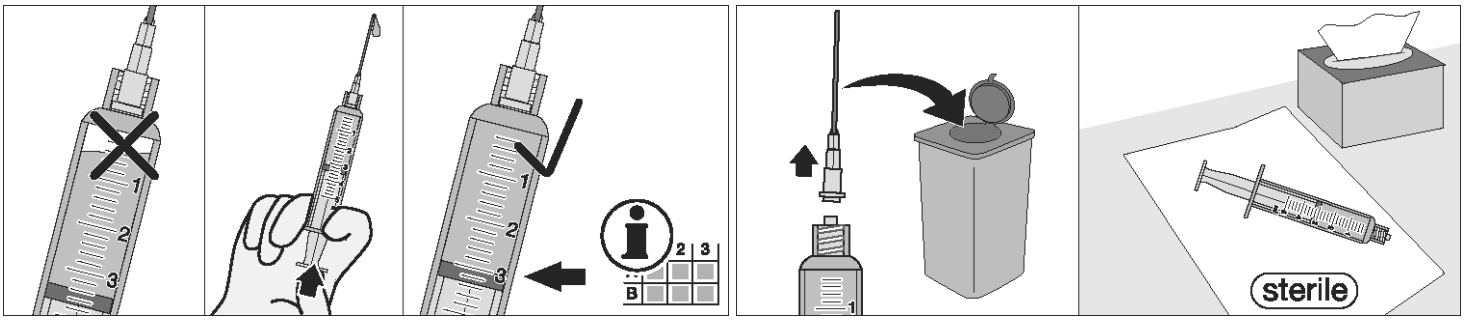
Do not disconnect.

D. Filling Dilution Syringe with Saline



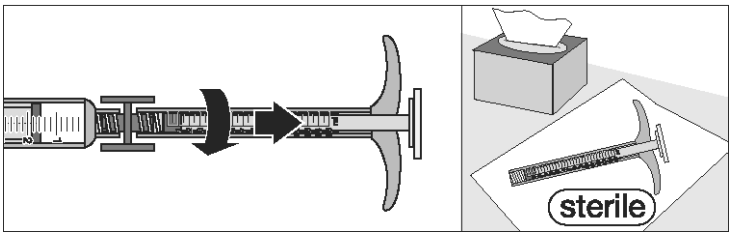
10. Open the saline solution vial.
11. Fit the second dilution syringe with a blunt 18G-needle (pink needle hub).
12. Use the blunt needle to withdraw the desired amount of saline (see dilution table) into the dilution syringe.

E. Disconnect Needle



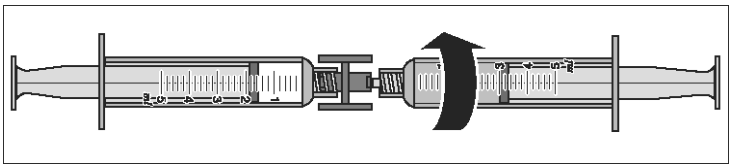
13. Remove all excess air – adjust to desired volume if necessary. Refer to dilution table above.
14. Disconnect the needle and discard.
15. Place the syringe filled with saline on a clean and disinfected surface.

F. Connect Dilution Syringes



16. Disconnect the RADIESSE® Injectable Implant syringe from the connector.
17. Place the RADIESSE® Injectable Implant syringe on a clean and disinfected surface – avoid contamination.

Do not discard the RADIESSE® Injectable Implant syringe, it will be used again!



18. Connect the dilution syringe filled with RADIESSE® Injectable Implant to the dilution syringe filled with saline.

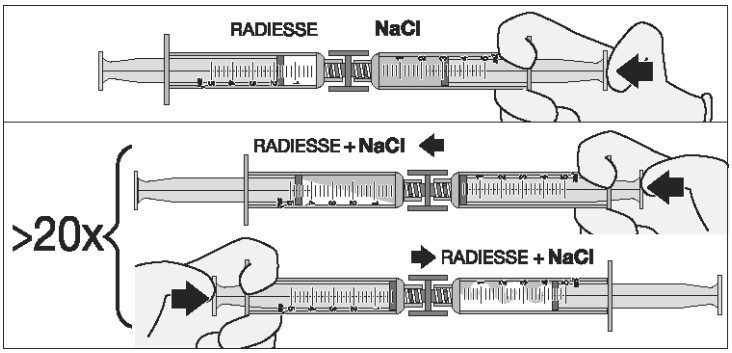
G. Dilution of RADIESSE® Injectable Implant and saline

Each mixing stroke is one complete compression of the first mixing syringe plunger followed by one complete compression of the second mixing syringe plunger. Plungers are compressed firmly and quickly.

1 mixing stroke = 2 pump moves (back and forth)

Mixing has to be repeated before every new transfer of product from mixing syringe to injection syringe.

H. Dilution of RADIESSE® Injectable Implant

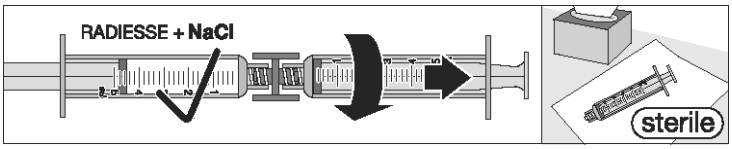


19. Mix the saline and RADIESSE® Injectable Implant by alternately depressing the plungers until the product is mixed homogenously (at least 20 mixing strokes).

1 mixing stroke = 2 pump moves

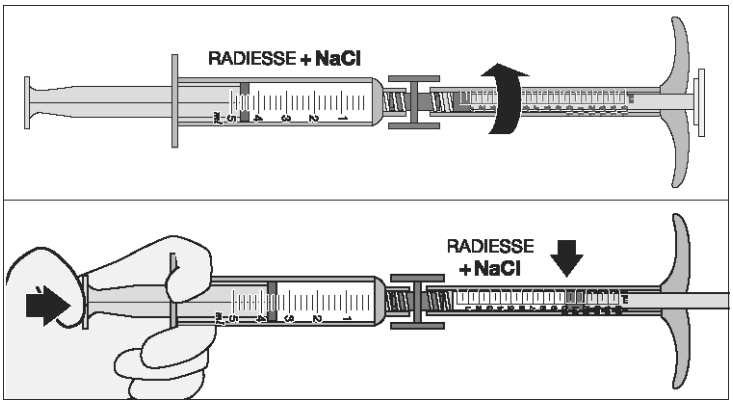
The formation of air bubbles in the dilution is normal.

I. Check for Homogeneity



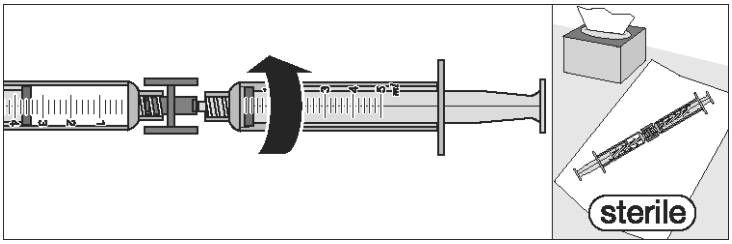
20. Check if the product is mixed homogenously – if necessary, mix again.
21. After mixing, please assure that the whole product is located in one syringe.
22. Remove the empty syringe from the connector and place it on a clean and disinfected surface.

J. Transfer into RADIESSE® Syringe



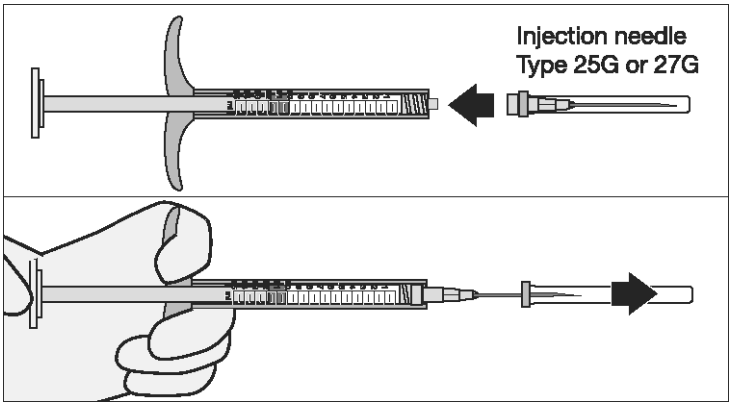
23. Connect the empty RADIESSE® Injectable Implant syringe to the connector and transfer the desired amount of product into the injection syringe by pushing the product into the empty syringe. (Injection with the mixing syringe would cause a too high finger force.)
    Mixing has to be repeated before every new transfer of product from mixing syringe to injection syringe (see last instruction step).

K. Avoid Contamination



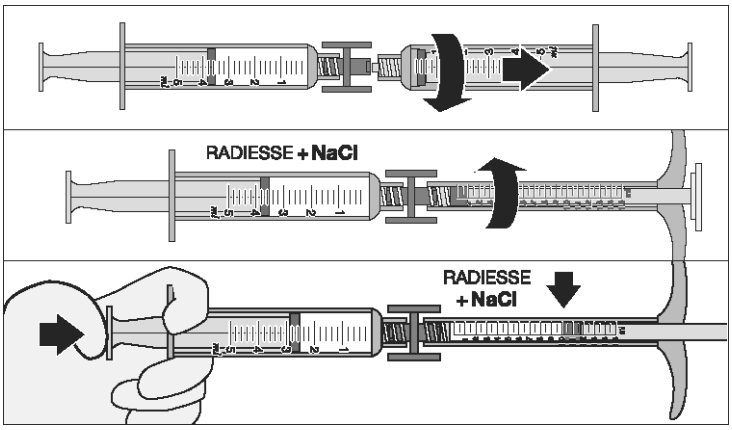
24. **To avoid contamination and dry out of the product please attach the empty 5 mL dilution syringe again to the RAPIDFILL Connector to close the syringe with the remaining product and place it on a clean and disinfected surface.**

L. Fit with needle/cannula and inject



25. Fit the RADIESSE® Injectable Implant syringe with an injection needle (27G x 3/4”) or cannula, blunt tip, 25G x 2” (0.5 x 50 mm).
26. Proceed with the injection.

M. Filling of the remaining product



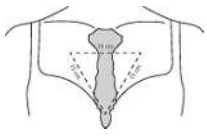
27. **If more product is needed repeat the mixing steps 19 to 26.**
Ensure that the product is homogenously mixed before transferring into Injection syringe.

Discard all components and all remaining product according to local regulations for potentially infectious and sharp materials.

9.3.5 Posology and Administration Method for Décolleté Treatment

- Prepare person for percutaneous injection using standard methods. The treatment injection site is to be prepared with a suitable antiseptic. Local or topical anesthesia could be applied at the injection site, ice could be applied to the area to decrease local swelling/distention, or sedation could be used at the discretion of the health care practitioner.
- It is recommended to perform the injection procedure with a 27G x 3/4” sharp needle or 25G x 50 mm blunt cannula.
- The injection needle or cannula has to be tightened securely to the syringe and primed with diluted 1:2 RADIESSE® Injectable Implant. If excess implant is on the surface of the Luer lock fittings, it needs to be wiped clean with sterile gauze.
- The syringe plunger can then slowly be pushed until the implant material extrudes from the end of the needle or cannula. If leakage is noted at the Luer fitting, it may be necessary to tighten the needle or cannula, remove the needle or cannula and clean the surfaces of the Luer fitting or, in extreme cases, replace both the syringe and the needle/cannula.
- The health care practitioner locates the initial site for the implant. The health care practitioner is not allowed to inject into scar tissue or into a blood vessel.
- Diluted RADIESSE® Injectable Implant 1:2 is to be injected in the subdermal plane sufficiently deep to prevent nodular formation at the surface of the skin or ischemia of the overlying tissue.
- Over-correction is not allowed.
- The injection of 4.5 mL of diluted 1:2 RADIESSE® Injectable Implant is in the central area of the décolleté in an area of approximately 100 cm^2 (see Figure 1), limited by an equilateral triangle of approximate side length up to 15 cm.

Figure 1: Treatment Area

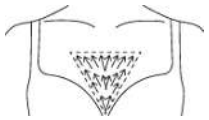


- If significant resistance is encountered when pushing the plunger, the needle/cannula can be moved slightly to allow easier placement of the material.
- If significant resistance is still encountered, the health care practitioner should pull the needle or cannula entirely out of the injection site and try again in a new position.
- If significant resistance continues to persist, the health care practitioner should try a different needle or cannula. If this is not successful, the syringe and needle/cannula should be replaced. The needle or cannula is to be advanced into the sub-dermis to the starting location; the plunger of the syringe is to be carefully pushed to start the injection by slowly injecting the implant material.

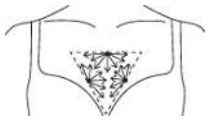
- The technique of retrograde linear threads has to be utilized (see Figure 2).

Figure 2: Linear threading retrograde technique when using 27G x 3/4" needle or 25G x 50 mm cannula (2).

Injection technique with needle:



Injection technique with cannula:



- The linear threading retrograde technique with using a 27G x 3/4" needle: beginning in the lower corner and moving from the medial line towards the lateral rim of the triangle (as shown on Figure 2), linear threads of 0.1 – 0.25 mL per thread has to be placed in a retrograde way in the sub-dermal plane. The procedure has to be repeated from the other body side. In whole, from 18 to 45 linear threads have to be placed in a retrograde way to cover the entire central décolleté area (up to 100 cm²) and to distribute evenly the RADIESSE® Injectable Implant volume of 4.5 mL.
- The linear threading retrograde technique with using 25G x 50mm cannula: three cannula entry points have to be made with a 23G pre-hole needle (see Figure 2). From each of the entry points, linear threads of 0.1 to 0.25 mL of diluted 1:2 RADIESSE® Injectable Implant per thread have to be placed in a retrograde way in the subdermal plane. In total, 18 to 45 linear threads have to be placed to cover the entire central décolleté area (up to 100 cm²) and to evenly distribute the RADIESSE® Injectable Implant volume of 4.5 mL.
- After every repeated transfer of diluted 1:2 RADIESSE® Injectable Implant from the mixing syringe into the injection RADIESSE® Injectable Implant syringe, another sterile needle or cannula has to be utilized and the used injection needles and cannulas must be discarded.
- Following treatment, manual massage of the entire treatment area has to be performed by the health care practitioner in order to promote even distribution of diluted 1:2 RADIESSE® Injectable Implant.

To achieve optimal results, a re-treatment is recommended at week 16 after initial treatment. If indicated, persons may be treated up to 3 times within 16 weeks.

The maximum treatment volume per treatment session is 4.5mL.

A maximum of 13.5 mL diluted 1:2 RADIESSE® Injectable Implant is recommended as maximum yearly dose, when treating the décolleté. The dose may be adapted according to the person's tissue, age and technique for implantation.

9.4 POST-ADMINISTRATION MONITORING

It is recommended, that the treated person should stay for a post-administration monitoring time in the premises of the health care practitioners, in order to identify any potential undesirable side-effects.

Persons should be instructed to report any side effects which last for more than one week and any adverse event as soon as it occurs to his/ her health care practitioner, especially if the person has changes in his/ her vision, signs of a stroke (including sudden difficulty speaking, numbness or weakness in his/ her face, arms, or legs, difficulty walking, face drooping, severe headache, dizziness, or confusion), white appearance of the skin, or unusual pain during or shortly after treatment. The health care practitioner may then refer the person to the appropriate treatment.

10 PATIENT COUNSELING INFORMATION

The patient should be instructed in appropriate post-procedural care, which may include the following, to promote normal healing and avoid complications.

- Apply ice or cool compresses to areas of injection for approximately 24 hours.
- Patients should not apply cosmetics to the treated area for at least 12 hours following injection. Additionally, patients are advised to avoid prolonged exposure to sun, ultraviolet (UV) rays, cold temperatures, or heat (e.g., sauna, steam rooms) for at least 24 hours post-injection.
- Massage area if palpable nodules become present.
- Promote facial rest for one week by encouraging patients to limit talking, smiling and laughing.
- Inform patient that postoperative swelling and numbness is common. Swelling will usually resolve within 7 to 10 days but may persist for several weeks. Numbness should resolve within 4 to 6 weeks.
- Provide oral analgesics and instruct patients to rinse the mouth with saline solution 4 to 6 times per day for 1 week postoperatively.

After décolleté treatment:

- Instruct the patient not to apply makeup 12 hours after injection, not to manipulate the décolleté and to minimize exposure of the treated area to extreme heat or cold for at least 24 hours after treatment.
- Advise the patient not to exercise strenuously, not to consume alcoholic beverages for 24 hours after treatment and to avoid prolonged exposure to natural or artificial sources of UV radiation (e.g., sunlight or tanning booth) in the décolleté.

11 STORAGE

Packaged RADIESSE® Injectable Implant should be stored at a controlled room temperature between 15° C and 32° C (59° F and 90° F). Keep dry and away from sunlight. Do not use if the expiration date has been exceeded. The expiration date is printed on the product labels.

12 DISPOSAL

Used and partially used syringes and injection needles could be biohazardous and should be handled and disposed of in accordance with facility medical practices and local, state or federal regulations.

13 Electronical IFU (eIFU) Information

A printable PDF version of the IFU in your local language can be found on the following website: www.ifu.merzaesthetics.com. For the most recent version of the IFU please always refer to the website. An update of the IFU may have happened due to safety reasons.

14 Training

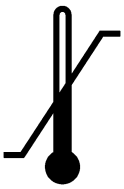
Training on RADIESSE® Injectable Implant is available upon request to your Merz Aesthetics contact or authorized distributor.

15 WARRANTY

Merz North America, Inc. warrants that reasonable care has been exercised in the design and manufacture of this product.

THIS WARRANTY IS IN LIEU OF AND EXCLUDES ALL OTHER WARRANTIES NOT EXPRESSLY SET FORTH HEREIN, WHETHER EXPRESSED OR IMPLIED BY OPERATION OF LAW OR OTHERWISE, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR ITS PARTICULAR PURPOSE.

Handling and storage of this product, as well as factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond Merz North America, Inc.'s control directly affect the product and the results obtained from its use. Merz North America, Inc.'s obligation under this warranty is limited to the replacement of this product and Merz North America, Inc. shall not be liable for any incidental or consequential loss, damage, or expense, directly or indirectly, arising from the use of this product. Merz North America, Inc. neither assumes, nor authorizes any person to assume for Merz North America, Inc., any other or additional liability or responsibility in connection with this product.

Symbol	Title of symbol
	Catalogue number
	Batch code
	Unique device identifier
	Use-by date
	Do not resterilize
	Do not use if package is damaged
	Temperature limit
	Single Use Do not re-use
	Consult electronic instruction for use
	Sterilized using steam or dry heat

Symbol	Title of symbol
	Sterilized using ethylene oxide

16 MANUFACTURED BY

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