MERZ NORTH AMERICA
Medical Affairs

RADIESSE® (Calcium Hydroxylapatite or CaHA) Injectable Implant
Application of Radiesse in Body Areas

Merz North America, Inc.

This Medical Information Letter is in response to your unsolicited question. Some information contained in this letter may be outside the approved *Instructions for Use*[1] for RADIESSE® Injectable Implant. This response is not intended to offer recommendations for administering RADIESSE® Injectable Implant in any manner inconsistent with its approved labeling.

Executive Summary

Radiesse Injectable Implant is approved by the United States Food and Drug Administration (FDA) and is indicated for the following:[1]

- Subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.
- Hand augmentation to correct volume loss in the dorsum of the hands.
- Restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

Radiesse Injectable Implant is a sterile, non-pyrogenic, semi-solid, cohesive implant. Its principle component is synthetic calcium hydroxylapatite (CaHA) suspended in a gel carrier of sterile water for injection, glycerin, and sodium carboxymethylcellulose. Each pre-filled, steam-sterilized syringe of Radiesse Injectable Implant (1.5cc, 0.8cc) has a CaHA particle-size range from 25 to 45 microns and should be injected with a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

This unique calcium-based injectable implant provides immediate volume correction in soft tissue, while inducing collagenesis in the treatment area. The treatment results can last up to a year or more in many patients.

Mixing Radiesse with Varying Amounts of Diluent

Highly diluted CaHA treatment has been reported to reduce skin laxity, in part due to the collagen-stimulating effects of CaHA.[2, 3] Some practitioners may dilute initially with lidocaine to reduce discomfort, adding normal saline solution to achieve further dilution.[2] Dilution can expand use of CaHA to treat areas of the body other than the face that require more product spread,[2] although this technique is not approved for this purpose and is considered off-label. Multiple studies have reported the effectiveness of CaHA mixed with varying amounts of diluent to tighten the skin and improve the appearance of the neck, décolletage, upper arms, abdomen, buttocks, thighs, breasts and knees.[3-7]

CaHA for Neck and Décolletage Skin Tightening

Injection of diluted CaHA was reported to be effective for skin tightening in a study that explored the ability of CaHA to stimulate collagen and elastin, in the neck and décolletage areas, without simultaneous volumization.[3] Twenty women with skin laxity in the neck and décolletage were treated with multiple, linear subdermal injections at baseline and 4 months. CaHA was diluted with preserved saline (1:2 dilution for normal skin, 1:4 for thin skin, and 1:6 for atrophic skin). The women also received deep subdermal CaHA injection (~0.1 ml) of the same dilutions in the periauricular area for skin biopsy to evaluate neocollagenesis at 4 and 7 months post injection.

Neocollagenesis in the periauricular area was comparable for all three dilutions. Collagen type I expression continued to increase after the second injection through 7 months ($p<0.00001$). Collagen type III expression peaked at 4 months ($p=0.00001$), then declined. Elastin expression followed a pattern similar to collagen type I, increasing at 4 ($p<0.05$) and 7 months ($p<0.00001$), peaking at 7 months. Cutometry results showed that skin elasticity significantly increased at 4 ($p<0.05$) and 7 months ($p<0.00001$). Neoangiogenesis increased at 4 ($p<0.0034$) and 7 ($p<0.00001$) months, suggesting that CaHA may also improve blood flow. Significant increases in dermal thickness were observed by ultrasound at 4 ($p<0.01$) and 7 months ($p<0.0001$). Patient-reported Global Aesthetic Improvement Scores were “much improved” at 4 (2.05 ± 0.51) and 7 months (2.55 ± 0.51), similar to physician-reported scores (1.90 ± 0.45 and 2.15 ± 0.37, respectively), where 1 is very much improved and 5 is worse. The procedure was well tolerated.

Diluted CaHA stimulated collagen and elastin synthesis, and increased neovascularization when injected into the skin of the neck and décolletage. The authors noted that the dermal remodeling was associated with increased dermal thickness, as well as improved elasticity and pliability.

CaHA for Neck and Décolletage Skin Tightening and Improvement in the Appearance of Lines

CaHA combined with micro-focused ultrasound with visualization (MFU-V) improved the appearance of neck and décolletage lines and wrinkles, in a retrospective study of 44 women and 3 men with skin laxity.[4] Patients received the combined treatment on the neck (n=29), décolletage (n=5), or both areas (n=13). CaHA 1.5 ml was diluted 1:1 with 1.5 ml of 2% lidocaine solution and injected with a 50 mm-long 25G cannula in a subdermal manner, placing micro-droplets using a fanning technique at four entry points along the neck and three along the décolletage. This technique allowed coverage of the same area as MFU-V, using one-half syringe of CaHA per side. Vigorous massage of treatment areas was done following injection to ensure an even dispersion of product in the treated area.

The mean neckline score improved from 2.6 at baseline (moderate-to-severe lines) to 1.3 (mild lines) 90 days after treatment ($p<0$ .001). The mean décolletage scores improved from 2.6 and 3.3 on the Merz Aesthetics and Fabi-Bolton scales, respectively, to 1.1 and 1.8 (mild wrinkles), 90 days after treatment ($p<0$ .001). Combined neck and décolletage patient satisfaction scores showed a statistically significant improvement from 3.2 ± 0.6 at baseline to 4.5 ± 0.6 after treatment ($p<$ 0.001). Mild pain (90%) and bruising (100%) were the only side effects noted.

CaHA for Tightening the Upper Arms and Abdomen

Dilute CaHA was found to be effective in tightening the skin of the upper arms and abdomen in two separate case series.[5] Ten women in each series received CaHA diluted 1:2 with normal saline solution and 2% lidocaine in the upper arms and CaHA diluted 1:4 with saline solution in the abdominal wall. Subdermal injections were administered using a short, linear-threading technique.

Upper arm skin elasticity increased from 72 U at baseline to 82 U at 3 months ($p\leq0.05$) by cutometry. Statistically significant increases in dermal thickness of the abdominal wall were observed by ultrasound (0.7 mm around the umbilicus and 0.4 mm around the sides of abdomen), with an overall dermal thickness increase of 26.7% from baseline ($p\leq0.05$). Overall, 90% of patients and physicians rated the improvement as good to very good. Treatment was reported to be well tolerated, with four cases of minor hematoma that resolved within one week of injection.

CaHA for Skin Tightening and Improvement of Cellulite Appearance on Buttocks and Thighs

Hyperdiluted CaHA combined with MFU-V improved skin laxity and the appearance of cellulite in a retrospective study of 20 women with buttock and thigh cellulite.[6] The women received 1.5 ml CaHA diluted 1:1 with 1.5 ml of 2% lidocaine solution immediately following MFU-V. One patient received six dilutions so neocollagenesis could be evaluated. The hyperdiluted CaHA (3 ml) was injected subdermally using a micro-droplet fanning technique (1 ml per buttock or thigh, 10 lines of 0.1 ml per line) to cover the same area as MFU-V. Vigorous massage of treatment areas was done to

ensure even dispersion of product in the treated area. Photographs taken at baseline and 90 days were evaluated by two independent evaluators, who were blinded to treatment.

The evaluators reported significant improvements at 90 days, versus baseline on each item of the cellulite severity scale ($p<0.001$). A 4.5 point improvement in mean overall score was noted after a single combined treatment ($p< 0.001$). Peak neocollagenesis at 90 days was observed with the 1:1 dilution. The highest conversion of collagen type III into type I was seen in CaHA samples diluted 1:1 and 1:0.6 (without subsequent MFU-V treatment). Ten women were very satisfied with the treatment and 9 were satisfied; 19 women indicated that their dimples appeared less visible. The procedures were reported to be well tolerated.

CaHA for Stretch Marks

Hyperdiluted CaHA, combined with micro-needling and topical ascorbic acid, was found to improve the appearance of stretch marks in 35 women presenting with red or white striae on the buttocks, thighs, knees, abdomen and breasts.[7] CaHA diluted 1:1 with 2% lidocaine was injected using a 23 gauge needle. This was followed immediately by micro-needling and topical application of 20% ascorbic acid, which was repeated after 1 and 2 months. A maximum of 3 ml of CaHA was injected per patient using a micro-bolus technique. Skin biopsies were obtained from one patient, who later underwent abdominoplasty.

Mean Manchester Scar Scale decreased from 12.0 (±0.8) at baseline to 7.1 (±1.4) 1 month after the final treatment, indicating significant improvement in the appearance of stretch marks ($p<0.001$). The women studied were very satisfied (n=22), satisfied (n=8), neither satisfied nor dissatisfied (n=4), or unsatisfied (n=1) with treatment results using a 5-point patient satisfaction scale. Scar Scale scores and patient satisfaction scores were significantly correlated ($r=0.483$; $p=0.003$). Biopsy results demonstrated increased quantity and quality of collagen and elastin fibers in areas treated with the combined therapy. No serious adverse events were noted. Two women developed post-inflammatory hyperpigmentation, which resolved after a 30 day course of whitening cream. Bruising (n=32) and erythema (n=35) resolved within 7 days.

Safety Information [1]

Contraindications:

- Patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Patients with known hypersensitivity to any of the components.
- Patients with bleeding disorders.

Warnings:

- Introduction of Radiesse injectable implant into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers. For example inject Radiesse injectable implant slowly and apply the least amount of pressure necessary. Rare but serious adverse events (AEs) 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. Stop the injection immediately if a patient exhibits any of the following symptoms: (*a*) changes in vision, (*b*) signs of a stroke, (*c*) blanching of the skin, or (*d*) 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.
- Use of Radiesse injectable implant in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- Injection procedure reactions have been observed consisting mainly of short-term (i.e., < 7 days) bruising, redness and swelling. Refer to adverse events sections for details.
- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of Radiesse injectable implant occurs.
- The safety and effectiveness for use in the lips has not been established. There have been published reports of nodules associated with the use of Radiesse injectable implant injected into the lips.

For full safety information, please visit www.Radiesse.com or call Merz North America, Inc., or call Customer Solutions at 1-844-469-6379. Please consult the Radiesse Injectable Implant *Instructions for Use* document, included with this letter, for full FDA-approved labeling and before starting treatment. [1]

In order for Merz North America, Inc., to monitor the safety of Radiesse, we encourage healthcare professionals to report adverse events or suspected overdoses to the Company at 1-844-469-6379. Please consult the *Instructions for Use* document for Radiesse.[1]

REFERENCES

1. Merz North America, Inc. RADIESSE® *Intructions for Use.* www.Radiesse.com
2. Van Loghem J, Yutskovaskaya Y, Werschler W. Calcium hydroxylapatite over a decade of clinical experience. *J Clin Aesthet Dermatol*. 2015;8(1):38-49.
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4. Casabona G, Nogueira Teixeira D. Microfocused ultrasound in combination with diluted calcium hydroxylapatite for improving skin laxity and the appearance of lines in the neck and décolletage. *J Cosmet Dermatol*. 2018;17(1):66-72.
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7. Casabona G, Marchese P. Calcium hydroxylapatite combined with microneedling and ascorbic acid is effective for treating stretch marks. *Plast Reconstr Surg Glob Open.* 2017;5:e1474.

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