RADIESSE® (+)

Lidocaine

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE

℞ ONLY

DEVICE DESCRIPTION

RADIESSE® (+) Lidocaine injectable implant (hereinafter referred to as RADIESSE® (+) injectable implant) is an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant, whose principal component is synthetic calcium hydroxylapatite suspended in a gel carrier of glycerin, sodium carboxymethylcellulose, 0.3% lidocaine hydrochloride and sterile water for injection. RADIESSE® (+) injectable implant (1.5cc and 0.8cc) has a calcium hydroxylapatite particle size range of 25–45 microns and should be injected with a 25 gauge Outer Diameter (O.D.) to 27 gauge Inner Diameter (I.D.) needle.

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.

CONTRAINDICATIONS

- RADIESSE® (+) is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- RADIESSE® (+) is not to be used in patients with known hypersensitivity to any of the components.
- RADIESSE® (+) injectable implant is not intended to be used in patients with known hypersensitivity to lidocaine or anesthetics of the amide type.
- RADIESSE® (+) injectable implant is contraindicated for patients with bleeding disorders.

WARNINGS

- Introduction of RADIESSE® (+) 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® (+) 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.
- 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.
- 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.
- Injection procedure reactions have been observed consisting mainly of short-term (i.e., <7 days) bruising, redness and swelling. Refer to the Adverse Events sections for details.

PRECAUTIONS

- In order to minimize the risks of potential complications, RADIESSE® (+) 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.
- The calcium hydroxylapatite (CaHA) particles of RADIESSE® (+) injectable implant are radiopaque and are clearly visible on CT Scans and may be visible in standard, plain radiography. Patients need to be informed of the radio-opaque nature of RADIESSE® (+) injectable implant, so that they can inform their primary care health professionals as well as radiologists. In a radiographic study of 58 patients, there was no indication of RADIESSE® injectable implant potentially masking abnormal tissues or being interpreted as tumors in CT Scans.
- Health care practitioners are encouraged to discuss all potential risks of soft tissue injections with their patients prior to treatment and ensure that the 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® (+). Standard precautions associated with injectable materials should be followed.
- Patients 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.
- 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.
- The long-term safety of RADIESSE® (+) injectable implant has not been investigated in clinical trials.
- Safety of RADIESSE® (+) injectable implant for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- The safety of RADIESSE® (+) injectable implant in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.
- The safety of RADIESSE® (+) injectable implant with concomitant dermal therapies such as epilation, UV irradiation, or laser, mechanical or chemical peeling procedures has not been evaluated in controlled clinical trials.
- Injection of RADIESSE® (+) injectable implant into patients with a history of previous herpetic eruption may be associated with reactivation of the herpes.
- No studies of interactions of RADIESSE® (+) injectable implant with drugs or other substances or implants have been conducted.
- Safety and effectiveness in the periorbital area has not been established.
- The patient should be informed that he or she should minimize exposure of the treated area to extensive sun or heat exposure for approximately 24 hours after treatment or until any initial swelling and redness has resolved.
- Universal precautions must be observed when there is a potential for contact with patient body fluids. The injection session must be conducted with aseptic technique.
- RADIESSE® (+) injectable implant is packaged for single patient use. Do not resterilize. Do not use if package is opened or damaged. Do not use if the syringe end cap or syringe plunger is not in place.
- To help avoid needle breakage, do not attempt to straighten a bent needle. Discard it and complete the procedure with a replacement needle.
- Do not reshield used needles. Recapping by hand is a hazardous practice and should be avoided.

- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.
- Care should be taken to determine the risk versus the benefit for patients with congenital methemoglobinemia, with glucose-6-phosphate dehydrogenase deficiencies, and with patients who are receiving concomitant treatment with methemoglobin-inducing agent

NASOLABIAL FOLDS

A. ADVERSE EVENTS

I. NASOLABIAL FOLDS PRE-MARKET CLINICAL TRIAL – RADIESSE® (WITHOUT LIDOCAINE)

Tables 1-4 contain the adverse events for 117 patients in a randomized, controlled study at 4 US investigational sites. Patients in the study received RADIESSE® injectable implant in one side of the face and a collagen dermal implant as the Control in the other side of the face. Adverse events reported in patient diaries during the 14 days after treatment are listed in Tables 1 and 2. Physician reported adverse events are those reported by Investigators and patients any time outside the 2 week diaries. Those adverse events are presented in Tables 3 and 4.

Table 1 PATIENT DIARY ADVERSE EVENTS
Reported Through Patient Diaries Number of Patients with at Least One Adverse Event
By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)
Ecchymosis	74 (63.2)	50 (42.7)
Edema	81 (69.2)	62 (53.0)
Erythema	78 (66.7)	84 (71.8)
Granuloma	0 (0.0)	0 (0.0)
Nodule	1 (0.9)	1 (0.9)
Pain	33 (28.2)	26 (22.2)
Pruritis	21 (18.0)	24 (20.5)
Other*	35 (29.9)	26 (22.2)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

There were 12 systemic adverse events reported for 9 patients. None of these systemic adverse events were related to either RADIESSE® injectable implant or Control and included emergency gallbladder surgery, breast pain, infected and exposed breast implant, gastroenteritis, uterine fibroids, headache, burning and numbness in tongue and lips, tongue ulceration and fatigue.

Table 2 PATIENT DIARY ADVERSE EVENTS
By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)	RADIESSE® Number of Days				CONTROL Number of Days			
			1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)	1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	91 (60.3)	60 (39.7)	16 (10.6)	37 (24.5)	33 (21.9)	5 (3.3)	15 (9.9)	29 (19.2)	12 (7.9)	4 (2.6)
Edema	104 (54.5)	87 (45.5)	34 (17.8)	43 (22.5)	17 (8.9)	10 (5.2)	34 (17.8)	39 (20.4)	10 (5.2)	4 (2.1)
Erythema	105 (45.1)	128 (54.9)	39 (16.7)	26 (11.2)	19 (8.2)	21 (9.0)	45 (19.3)	35 (15.0)	16 (6.9)	32 (13.7)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Pain	40 (54.8)	33 (45.2)	22 (30.1)	13 (17.8)	4 (5.5)	1 (1.4)	20 (27.4)	10 (13.7)	2 (2.7)	1 (1.4)
Pruritis	24 (47.1)	27 (52.9)	15 (29.4)	5 (9.8)	3 (5.9)	1 (2.0)	11 (21.6)	10 (19.6)	3 (5.9)	3 (5.9)
Other*	52 (56.5)	40 (43.5)	15 (16.3)	7 (18.5)	8 (8.7)	12 (13.0)	8 (8.7)	10 (10.9)	11 (12.0)	11 (12.0)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

Table 3 PHYSICIAN REPORTED ADVERSE EVENTS
Number of Patients with at Least One Adverse Event
By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)
Ecchymosis	0 (0.0)	2 (1.7)
Edema	5 (4.3)	4 (3.4)
Erythema	6 (5.1)	9 (7.7)
Granuloma	0 (0.0)	0 (0.0)
Needle Jamming	1 (0.9)	0 (0.0)
Nodule	0 (0.0)	2 (1.7)
Pain	2 (1.7)	1 (0.9)
Pruritis	1 (0.9)	2 (1.7)
Other*	3 (2.6)	3 (2.6)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

Table 4 PHYSICIAN REPORTED ADVERSE EVENTS
By Adverse Event Type N = 117

ADVERSE EVENT TYPE	RADIESSE® Total Reporting Symptoms N (%)	CONTROL Total Reporting Symptoms N (%)	RADIESSE® Number of Days				CONTROL Number of Days			
			1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)	1-3 N (%)	4-7 N (%)	8-14 N (%)	>14 N (%)
Ecchymosis	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
Edema	5 (41.7)	7 (58.3)	5 (41.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (41.7)	0 (0.0)	0 (0.0)	2 (16.7)
Erythema	9 (42.9)	12 (57.1)	4 (19.0)	2 (9.5)	2 (9.5)	1 (4.8)	2 (9.5)	3 (14.3)	4 (19.0)	3 (14.3)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)
Pain	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Other*	4 (50.0)	4 (50.0)	1 (12.5)	0 (0.0)	2 (25.0)	1 (12.5)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)

* "Other" adverse events for both RADIESSE® injectable implant and Control include soreness, numbness, contour irregularity, tenderness, and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

II. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

A post approval study was performed to 1) collect long-term safety information on use of RADIESSE® injectable implant injected into the nasolabial folds; and 2) to assess the effect of multiple injections. There were no reports of long term adverse events in this post approval study. The adverse events monitored in the post-approval study included allergic reaction, ecchymosis, edema, embolization, erosion, erythema, extrusion, granuloma, hematoma, infection, necrosis, needle jamming, nodule, and pain.

III. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY – RADIESSE® WITHOUT LIDOCAINE

Adverse events reported in the short-term Fitzpatrick Skin Type IV-VI post-approval study are presented in Table 5.

Table 5 ADVERSE EVENTS
N = 100

ADVERSE EVENT TYPE	PATIENTS REPORTING SYMPTOMS N (%)
Hypertrophic Scarring	0 (0.0)
Keloid Formation	0 (0.0)
Hypopigmentation	0 (0.0)
Hyperpigmentation-Upper Lip	1 (1.0)
Hyperpigmentation-Other	0 (0.0)
Bumpiness	1 (1.0)
Ecchymosis	7 (7.0)
Eczema on Leg	1 (1.0)
Edema	12 (12.0)
Erythema	16 (16.0)
Eye Stye	1 (1.0)
Mild Bleeding at Injection Site	1 (1.0)
Needle Jamming	1 (1.0)
Tenderness	2 (2.0)
Urinary Tract Infection	1 (1.0)

IV. NASOLABIAL FOLDS PRE-MARKET CLINICAL TRIAL – RADIESSE® (+) (RADIESSE® WITH 0.3% LIDOCAINE)

Tables 6 and 7 contain the adverse events for 101 subjects in a randomized, controlled study at 3 Canadian investigational sites. Patients in the study received RADIESSE® (+) injectable implant in one nasolabial fold (Treatment) and RADIESSE® injectable implant in the other nasolabial fold (Control). The adverse events reported during this study were generally expected, mild in nature and short in duration. The majority of adverse events were reported through the subject diaries.

Table 6 summarizes the number of adverse events reported in the subject diaries. Swelling and redness were the most frequently reported adverse events. There was no significant difference in adverse event rates between the nasolabial folds with RADIESSE® (+) injectable implant and the nasolabial folds with RADIESSE® injectable implant. Needle jams occurred during the injection of the RADIESSE® (+) injectable implant in three (3/101, 3%) subjects. In all cases, the needle was replaced and the RADIESSE® (+) injectable implant injections were completed without further sequelae.

No vascular compromise events occurred in the RADIESSE® (+) injectable implant injections.

In the RADIESSE® injectable implant injections, two (2/101, 2%) vascular compromise events occurred, requiring treatment to resolve.

Table 6 Adverse Events Reported in Subject Diaries Over the 4-Week Study Period
n = 202 Folds

Event Type*	n (%)	
	RADIESSE® (+) n = 101 Folds	**RADIESSE®** n = 101 Folds
Bruising	44 (43.6%)	48 (47.5%)
Itching	37 (36.6%)	34 (33.7%)
Pain	48 (47.5%)	57 (56.4%)
Redness	66 (65.3%)	71 (70.3%)
Swelling	90 (89.1%)	92 (91.1%)
Blanching	5 (5.0%)	8 (7.9%)

* "Other" adverse events reported by 19 subjects for both RADIESSE® injectable implant and Control include numbness, tenderness, lumps, bumps and discomfort.

Of the 13 blanching events described in Table 6, two were associated with previously described vascular compromise events. The remaining 11 were not determined to be vascular compromise events.

Table 7 summarizes the number of adverse events reported by the investigators. As with the patients, swelling and redness were the most frequently reported adverse events.

Table 7 Adverse Events Reported by Investigators
N = 101 Subjects

Event Type*	N (%)	
	RADIESSE® (+)	RADIESSE®
Bruising	20 (19.8%)	18 (17.8%)
Swelling	58 (57.4%)	55 (54.5%)
Erosion	0	1 (1.0%)**
Redness	51 (50.5%)	50 (49.5%)
Infection	1 (1.0%)†	0
Needle Jamming	3 (3.0%)‡	0
Nodule	0	0
Pain	0	1 (1.0%)
Vascular Compromise	0	1 (1.0%)

* "Other" adverse events for both RADIESSE® injectable implant and Control include tenderness and tingling sensation.
** Associated with vascular compromise event
† Herpes simplex infection unrelated to study device
‡ Returned product evaluation regarding one subject concluded that needle jam might have resulted from needle incompletely screwed onto the RADIESSE syringe's luer threads.

B. CLINICAL STUDIES

I. NASOLABIAL FOLD PRE-MARKET CLINICAL TRIAL – RADIESSE® (WITHOUT LIDOCAINE)

Study Design

The safety and effectiveness of RADIESSE® injectable implant for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. Patients were randomized to receive RADIESSE® injectable implant in one fold and a commercially available collagen implant in the contralateral fold.

Patients were eligible to receive up to three injections during the initial treatment phase (week 0, week 2 and week 4). At 2 weeks after each treatment, the level of correction was determined and if correction was less than optimal, the Investigator re-treated the nasolabial fold using the same respective treatment materials as in the initial treatment. A safety follow-up was conducted 1 month after any injection and at 3 and 6 months after the last injection. Effectiveness evaluations were conducted at 3 and 6 months after the last injection. Three blinded reviewers independently evaluated the severity of the subject's nasolabial folds using a validated 6-point wrinkle severity scale.

Study Endpoints

The primary effectiveness endpoint of the study was the blinded reviewers' Lemperle Rating Scale (LRS) score of wrinkle severity at 3 months after the last touch-up (at which optimal correction was achieved). In this assessment, LRS scores were determined, (using this validated 6-point scale), via blinded, photographic assessments by 3 board certified physicians. A change in LRS of 1 was considered to be clinically significant. Secondary effectiveness endpoints included the blinded reviewers' assessment of wrinkle severity at 6 months after treatment, and the volume of material injected.

Study Population

A total of 117 subjects (31-76 years of age) were randomized and treated and 115 (98.3%) completed the 3 month primary effectiveness evaluation and 113 (96.6%) completed the 6 month follow-up visit. The baseline demographics of the study population are presented in Table 8 which shows that the study enrolled a population of predominantly female, Caucasian non-smokers.

Table 8 PATIENT DEMOGRAPHICS
N = 117

AGE (YEARS)	
Mean	54.7
Standard Deviation	8.9
Minimum	31.0
Maximum	76.0
GENDER	
Female	105 (89.7%)
Male	12 (10.3%)
RACE	
American Indian	0 (0.0%)
Asian	0 (0.0%)
Black	2 (1.7%)
Caucasian	102 (87.2%)
Hispanic	11 (9.4%)
Other	2 (1.7%)
SMOKING HISTORY	
Quit Smoking	26 (22.2%)
Never Smoked	83 (70.0%)
Smokes	8 (6.8%)

Treatment Material Delivered

Volumes injected during the initial treatment phase are detailed in Table 9. The total mean volume for RADIESSE® injectable implant was 1.2 mL and 2.4 mL for the Control.

Table 9 TOTAL VOLUME OF MATERIAL INJECTED (mL)
N = 117

	RADIESSE®	CONTROL
Mean	1.2	2.4
Median	1.1	2.2
Standard Deviation	0.5	0.9
Minimum	0.3	0.8
Maximum	2.7	4.7

Effectiveness Results:

Table 10 contains the mean LRS at baseline, 3 months and 6 months for the RADIESSE® injectable implant treated nasolabial folds and the Control treated nasolabial folds with the difference between the means. Baseline scores for the RADIESSE® injectable implant and Control groups were not statistically different.

Table 10 COMPARISON OF MEAN LRS SCORES*
FOR RADIESSE® INJECTABLE IMPLANT AND CONTROL

	RADIESSE®	CONTROL	DIFFERENCE
Baseline	3.4	3.4	0.0
3 Months	1.9	3.5	1.6
6 Months	2.1	3.4	1.3

* Grading Scale: 0 = No wrinkles, 1 = Just perceptible wrinkle, 2 = Shallow wrinkle, 3 = Moderately deep wrinkle, 4 = Deep wrinkle, well-defined edges, 5 = Very deep wrinkle, redundant fold

Primary Effectiveness Endpoint

The primary effectiveness endpoint was to use mean LRS scores to evaluate whether RADIESSE® injectable implant was non-inferior to Control for the correction of nasolabial folds 3 months after final treatment. At 3 months, 84.6% of the RADIESSE® injectable implant treated nasolabial folds were scored at least 1-point higher than the Control, 12.8% were scored equally, and 2.6% were scored at least 1-point lower than the Control. RADIESSE® injectable implant met the statistical criteria for non-inferiority to Control at 3 months ($p<0.0001$), however, the Control scored no effectiveness at 3 months.

Secondary Effectiveness Endpoint

The pre-specified secondary superiority analyses at 6 months required a mean 1-point LRS difference between the improvements for the RADIESSE® injectable implant treated nasolabial fold versus improvement on the Control treated nasolabial fold and that in at least 50% of patients, the RADIESSE® injectable implant treated nasolabial fold be superior to the Control treated nasolabial fold. At 6 months after optimal correction was achieved, 78.6% of the RADIESSE® injectable implant treated nasolabial folds were scored at least 1-point higher than the Control-treated folds, 16.2% were scored equally, and 5.1% were scored at least 1-point lower than the Control. The mean LRS for the RADIESSE® injectable implant treated nasolabial folds demonstrated superiority when compared to the mean LRS for the Control-treated nasolabial folds at 6 months ($p< 0.0001$).

II. NASOLABIAL FOLDS LONG-TERM SAFETY POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

Study Objective

A post approval study was performed to 1) collect long-term safety information on use of RADIESSE® injectable implant injected into the nasolabial folds; and 2) to assess the effect of multiple injections.

Study Design

RADIESSE® injectable implant was assessed in a prospective, open-label, multi-center study of patients whose nasolabial folds were corrected with RADIESSE® injectable implant. 102 subjects (drawn from the 117 patients who participated in the premarket clinical trial) agreed to participate in the post approval study. Patients were requested to return for visits a minimum of 2 years and then a minimum of 3 years after their initial injection. At the beginning of the post marketing study, 8 patients were already 3 years from initial injection and, therefore, required only one visit. One hundred and two (102) patients were assessed a minimum of 2 years after initial injection and 99 were assessed a minimum of 3 years after initial injection. Three (3) patients were lost to follow up.

Study Population

The patient cohort in this post approval study was the continued follow-up of the pre-market cohort. Patient demographics are provided in Table 11.

Table 11 PATIENT DEMOGRAPHICS
N =102

AGE (YEARS)	
Mean	55.1
Standard Deviation	8.8
Minimum	31.0
Maximum	76.0
GENDER	
Female	94 (92.2%)
Male	8 (7.8%)
RACE	
American Indian	1 (1.0%)
Asian	0 (0.0%)
Black	1 (1.0%)
Caucasian	87 (85.3%)
Hispanic	11 (10.8%)
Other	2 (2.0%)
SMOKING HISTORY	
Quit Smoking	23 (22.6%)
Never Smoked	73 (71.6%)
Smokes	6 (5.9%)

The inclusion criterion for the study was participation in the pre-market clinical trial (Section I of the Nasolabial Folds CLINICAL STUDIES section) and signing a written informed consent for participation in the post-approval study. There were no additional exclusion criteria.

Study Endpoints

To collect long-term safety information of RADIESSE® injectable implant injected into the nasolabial folds at a minimum of 2 and 3 years after initial injection and to assess the effect of multiple injections.

Study Results

102 study patients and 204 folds received a mean of 3.7 and 1.8 RADIESSE® injectable implant injections, respectively, from the time period covering initial pre market study injection through the last post approval study visit. 100% of patients and 98% of folds received RADIESSE® injectable implant treatment during the same time period with only 11% of patients receiving RADIESSE® injectable implant injections during the post approval study period alone. During the post approval study, 15% of patients received Botulinum toxin injections and 9% of patients received facial dermal fillers other than RADIESSE® injectable implant in the nasolabial folds.

With respect to the long term safety of RADIESSE® injectable implant, there were no reports of long term adverse events in this post approval study. The adverse events monitored in the post-approval study included allergic reaction, ecchymosis, edema, embolization, erosion, erythema, extrusion, granuloma, hematoma, infection, necrosis, needle jamming, nodule, and pain. These results demonstrate the long term safety and effectiveness of RADIESSE® injectable implant up to 3 years after the date of first injection.

Study Limitations

RADIESSE injectable implant was studied in a limited number of predominately female patients. Safety of the RADIESSE® injectable implant following the correction of nasolabial folds beyond 3 years was not studied.

III. NASOLABIAL FOLDS FITZPATRICK SKIN TYPE IV-VI POST-APPROVAL STUDY – RADIESSE® (WITHOUT LIDOCAINE)

Study Objective

A post-approval study was performed to assess the safety of RADIESSE® injectable implant following correction of the nasolabial folds in patients with Fitzpatrick Skin Types IV, V, or VI, specifically to assess the likelihood of hypertrophic scarring, keloid formation and hyper- or hypopigmentation.

Study Design

The safety of RADIESSE® injectable implant was assessed in a prospective, open-label, multi-center study in 100 patients with Fitzpatrick Skin Types IV, V or VI whose nasolabial folds were corrected with subdermal injections of RADIESSE® injectable implant.

Study Population

Patient demographics are provided in Table 12.

Table 12 PATIENT DEMOGRAPHICS
N = 100

AGE (YEARS)	
Mean	52
Standard Deviation	11.1
Minimum	25
Maximum	78
GENDER	
Male	6 (6.0%)
Female	94 (94.0%)
RACE	
Caucasian	0 (0.0%)
Black	85 (85.0%)
Hispanic	12 (12.0%)
Asian	2 (2.0%)
Other	1 (1.0%)
FITZPATRICK SKIN TYPE	
IV	24 (24.0%)
V	35 (35.0%)
VI	41 (41.0%)
INJECTION VOLUME (mL)	
Mean	1.24
Standard Deviation	0.397
Minimum	0.6
Maximum	2.8

The inclusion criteria for the post-approval study were that the patient was at least 18 years of age, was Fitzpatrick Skin Type IV, V, or VI, and understood and accepted the obligation not to receive any other procedures or treatments in the nasolabial fold for 6 months.

The exclusion criteria for the post-approval study were that the patient had a history of hyper- or hypo-pigmentation in the nasolabial folds, keloid formation, or hypertrophic scarring, had a known bleeding disorder or was receiving drug therapy that could increase the risk of bleeding, had nasolabial folds that are too severe to be corrected in one treatment session, had received any dermal filler or other injections, grafting or surgery in either nasolabial fold, is pregnant, lactating, or not using acceptable contraception.

Study Endpoints

The likelihood of hypertrophic scarring, keloid formation and hyper- or hypopigmentation was evaluated through 6 months from treatment with RADIESSE® injectable implant in the nasolabial folds.

Length of Follow-up and Assessments

Patients were followed for 6 months from RADIESSE® injectable implant treatment (injection visit). Ninety days (90) ± 30 days from the injection visit, patients returned for a safety assessment of their nasolabial folds (3 month visit). One hundred eighty days (180) ± 30 days from the initial injection, patients returned for a safety assessment of their nasolabial folds (6 month visit).

Subject Accountability

One hundred (100) patients were enrolled in the post-approval study and assessed at the 3 month visit (100% follow-up rate). Ninety eight (98) patients were assessed at the 6 month visit (98% follow-up rate). Two patients were lost to follow-up.

Study Results

At 3 months, 100% of patients were assessed and there were no reports of hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site. At 6 months 98% of patients were assessed. Two patients were lost to follow-up. Of the 98 patients assessed, no occurrence of hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site was reported. One patient reported erythema in the upper left nasolabial fold that was treated with hydrocortisone and lasted for 111 days. Another patient experienced mild hyperpigmentation in the upper lip that lasted 159 days. No treatment was required.

The use of RADIESSE® injectable implant did not cause hypertrophic scarring, keloid formation, hyperpigmentation or hypopigmentation at the injection site in persons with Fitzpatrick Skin Types of IV, V, and VI in this study throughout the follow-up period of 6 months.

Study Limitations

RADIESSE® injectable implant was studied in a limited number of predominately female patients. Likelihood of keloid formation, hypertrophic scarring, and hypo- or hyperpigmentation after use of RADIESSE® injectable implant for the correction of nasolabial folds in patients with Fitzpatrick Skin Type 4, 5 and 6 beyond 6 months was not studied.

IV. NASOLABIAL FOLD PRE-MARKET CLINICAL TRIAL – RADIESSE® (+) (RADIESSE WITH 0.3% LIDOCAINE)

Study Design

The safety and effectiveness of RADIESSE® (+) injectable implant for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. The primary objective of the study was to assess pain control when RADIESSE® containing lidocaine was used to treat nasolabial folds.

Subjects were randomized to receive RADIESSE® (+) injectable implant in one fold and the commercially available RADIESSE injectable implant (Control), in the contralateral fold.

Effectiveness evaluations were conducted at 15, 30, 45, and 60 minutes after injection; and at 1, 2, and 4 weeks after injection. At weeks 1, 2, and 4, subjects returned for a pain assessment using the 10 cm visual analog scale (VAS) and a safety assessment by the blinded assessing physician. Aesthetic outcomes were assessed by the blinded assessing investigator using the validated Merz Nasolabial Fold Scale and the Global Aesthetic Improvement Scale (GAIS).

Study Endpoints

The primary effectiveness endpoint of the study was to assess whether there was a statistically significant reduction in pain in the nasolabial fold injected with RADIESSE® (+) injectable implant compared to the nasolabial fold injected with RADIESSE® injectable implant immediately after treatment using the visual analog pain scale (VAS).

There were five secondary effectiveness endpoints that (1) evaluated whether the difference of nasolabial fold pain when injected with RADIESSE® (+) injectable implant versus RADIESSE® injectable implant (without lidocaine) was clinically meaningful immediately after treatment (defined as a minimum of 2.0 cm reduction on the VAS); (2) assessed pain in the nasolabial fold treated with RADIESSE® (+) compared to the assessed pain in the nasolabial fold treated with RADIESSE® at 15, 30, 45, and 60 minutes, and at 1, 2, and 4 weeks after treatment using the VAS; (3) assessed aesthetic effectiveness by a blinded assessing investigator at 1, 2, and 4 weeks after nasolabial fold treatment using the validated Merz Nasolabial Fold Scale and the Global Aesthetic Improvement Scale (GAIS); (4) assessed subject preference with respect to pain 60 minutes after treatment; and (5) assessed subject preference with respect to aesthetic outcome 1, 2, and 4 weeks after nasolabial fold correction.

Study Population

Table 13 presents subject demographics which show that most subjects were female and Caucasian. Eighteen percent of subjects enrolled were fairly evenly distributed across Fitzpatrick Skin Types (FST) IV, V, and VI.

Table 13.Subject Demographics
N = 102 Subjects

AGE (years)	
Mean (SD, Range)	48.85 (9.43, 30 - 77)
GENDER – N (%)	
Female	87 (85.3%)
Male	15 (14.7%)
RACE – N (%)	
Caucasian	88 (86.3%)
African American	8 (7.8%)
Hispanic	2 (2.0%)
Asian	1 (1.0%)
Other	3 (2.9%)
FITZPATRICK SKIN TYPE – N (%)	
I	6 (5.9%)
II	19 (18.6%)
III	59 (57.8%)
IV	8 (7.8%)
V	5 (4.9%)
VI	5 (4.9%)

Treatment Material Delivered

The volume of filler injected in each fold is detailed in Table 14 showing that the volume injected between the two products was nearly identical.

Table 14 Injection Volumes (cc)
n = 202 Folds

	n (%)	
	RADIESSE® (+) n = 101 Folds	**RADIESSE®** n = 101 Folds
Mean (cc) (SD, Range)	0.84 (0.32, 0.2 -1.5)	0.83 (0.34, 0.25 -1.8)

Effectiveness Results:

Primary Effectiveness Endpoint

The difference of the visual analog pain scale (VAS) scores between the two groups showed a statistically significant reduction in pain with RADIESSE® (+) compared to RADIESSE® (p-value <0.0001).

Secondary Effectiveness Endpoints

The first of five secondary effectiveness endpoints was to assess whether the difference in pain in the nasolabial fold treated with RADIESSE® (+) versus the nasolabial fold treated with RADIESSE® was clinically meaningful immediately after treatment (defined as a minimum of 2.0 cm reduction on the VAS). This analysis showed that in 91 of 101 subjects VAS scores were ≥ 2.0 cm lower for RADIESSE® (+) compared to RADIESSE® in a given subject, demonstrating a clinically meaningful reduction in pain that was statistically significant (p-value < 0.0001).

The second secondary effectiveness endpoint was to assess pain in the nasolabial fold injected with RADIESSE® (+) compared to the nasolabial fold injected with RADIESSE® at 15, 30, 45, and 60 minutes and 1, 2 and 4 weeks after treatment using the VAS. This analysis showed that for all of these time-points there was a statistically significant difference in pain with RADIESSE® (+) compared to RADIESSE®.

The third secondary effectiveness endpoint was to assess aesthetic improvement on the GAIS and the Merz Nasolabial Fold Scale at 1, 2, and 4 weeks post treatment by the blinded assessing investigators. The vast majority of subjects were improved on the GAIS and there were no statistical differences between the two groups with respect to GAIS improvement. There were no significant differences between RADIESSE® (+) and RADIESSE® on the Merz Nasolabial Fold Scale. The RADIESSE® (+) and the RADIESSE® ratings on the Merz Nasolabial Fold Scale were improved from baseline condition. These results were the same across all time-points.

The fourth secondary effectiveness endpoint was to assess subject pain preference at time zero. These data showed that 98 subjects (97%) indicated that one treatment was less painful than the other and 87 subjects (88%) determined the difference in pain level was significant enough to affect their preference for one dermal filler versus the other. Of the 87 subjects who indicated that the difference in pain levels would affect treatment preference, 86/87 had lower VAS scores with RADIESSE® (+).

The fifth secondary effectiveness endpoint was for study subjects to assess preference with respect to aesthetic outcome 1, 2, and 4 weeks after nasolabial fold correction. Less than half of subjects stated that one nasolabial fold looked better at any of these post-treatment time-points. Of those, only half stated that the aesthetic preference was significant enough to choose one treatment over the other.

OTHER SHORT TERM AND LONG TERM RADIOGRAPHIC EVALUATION — RADIESSE® (WITHOUT LIDOCAINE)

RADIESSE® (+) injectable implant and RADIESSE® injectable implant contain calcium hydroxylapatite particles (25-45 microns) that are radiopaque. A radiographic study was conducted to assess the radiographic appearance of RADIESSE® injectable implant in patients with both short-term and long-term follow-up after injection for HIV-associated facial lipoatrophy and treatment of nasolabial folds. The radiographic assessment consisted of standard, plain radiography and CT scanning. X-rays and CT Scans were assessed by two blinded, licensed radiologists. The inclusion of these patients allowed assessment of patients immediately after initial injection, at least 12 months after initial injection, and patients with varying volumes implanted.

A total of 58 patients in three patients groups were enrolled into the study. RADIESSE® injectable implant was determined to be visualizable in the X-ray radiographs by both evaluators, but the X-ray readings were not conclusive for the presence of the implant, when in fact it was present. This may be due to the fact that the volume of RADIESSE® injectable implant in some patients was small and the sensitivity of X-ray imaging may not be sufficient to detect small volumes of implant. RADIESSE® injectable implant was more readily visualizable by CT scan when compared to X-ray, and the CT scan results were read more consistently between two evaluators. RADIESSE® injectable implant was easily seen when imaging was done soon after an injection and was also seen when imaging was done several months after injection (minimum of 12 months). As expected, the results of the CT scan provided a superior image capability as compared to X-ray when visualizing RADIESSE® injectable implant (without lidocaine).

POST MARKETING SURVEILLANCE

The following adverse events have been identified during post-approval use of RADIESSE. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to RADIESSE. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to RADIESSE: infection, cellulitis, impetigo, loss of effect, product displacement/ migration, allergic reaction, anaphylaxis, hives, rash, pruritus, urticaria, angioedema, inflammation, necrosis, granuloma, nodules, induration, erythema, skin discoloration, pustule, skin pallor, hair loss, paresthesia, ptosis, pain, headache, swelling, asymmetry, abscess, herpetic infection including herpes simplex and herpes zoster, hematoma, blanching, blistering, dizziness, festoons, flu-like symptoms, Guillain-Barre syndrome, tachypnea, ischemic reaction, lymphoid hyperplasia, nausea, pericarditis, scarring, sensitivity to cold, vascular occlusion/obstruction, vascular compromise, ocular ischemia, diplopia, visual impairment/blindness, facial muscle paralysis, Bell's palsy.

The following interventions have been reported: antibiotics, anti-inflammatories, corticosteroids, anti-histamines, 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 an adverse event or an exhaustive list of possible interventions. Physicians 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.

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 with RADIESSE® (+) injectable implant will vary between patients. In some instances, additional treatments may be necessary depending on the size of the defect and the needs of the patient.

DIRECTIONS FOR USE

General

The following is required for the percutaneous injection procedure:

- RADIESSE® (+) injectable implant syringe(s)
- 25 gauge OD - 27 gauge ID needle(s) with Luer lock fittings

1. Prepare patient for percutaneous injection using standard methods. The treatment injection site should be marked and prepared with a suitable antiseptic.
2. Prepare the syringes of RADIESSE® (+) injectable implant 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.
3. Remove foil pouch from the carton. Open the foil pouch by tearing at the notches (marked 1 and 2), and remove the syringe from the foil pouch. 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.
4. 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).
5. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle. The syringe of RADIESSE® (+) injectable implant can then be twisted onto the Luer lock fitting of the needle taking care not to contaminate the needle. Discard needle package. **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 RADIESSE® (+) injectable implant 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.
6. Locate the initial site for the implant. Scar tissue and cartilage may be difficult or impossible to treat. Avoid if possible, passing through these tissue types when advancing the injection needle.
7. The amount injected will vary depending on the site and extent of the restoration or augmentation desired. RADIESSE® (+) injectable implant should be injected subdermally.
8. Use a 1:1 correction factor. No overcorrection is needed.
9. Insert needle with bevel down at approximately a 30° angle to the skin. Needle should slide under the dermis to the point you wish to begin the injection. This should be easily palpable with the non-dominant hand.
10. 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. Needle jams are more likely with use of needles smaller than 27 gauge ID.
11. Advance the needle into the subdermis to the starting location. Carefully push the plunger of the RADIESSE® (+) injectable implant syringe to start the injection and slowly inject the implant material in linear threads while withdrawing the needle. Continue placing additional lines of material until the desired level of correction is achieved.
12. Apply slow continuous even pressure to the syringe plunger to inject the implant as you withdraw the needle. The implant material should be completely surrounded by soft tissue without leaving globular deposits. The injected area may be massaged as needed to achieve even distribution of the implant.
13. Use once and discard in accordance with local safety standards.

PATIENT COUNSELING INFORMATION

Refer to the RADIESSE® (+) injectable implant Patient Information Guide.

STORAGE

RADIESSE® (+) injectable implant should be stored at a controlled room temperature between 15°C and 32°C (59°F and 90°F). The expiration date, when stored in these temperatures, is two years from date of manufacture. Do not use if the expiration date has been exceeded.

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.

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.

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MANUFACTURED BY
Merz North America, Inc.
4133 Courtney St., Suite 10
Franksville, WI 53126 USA
Telephone: (866) 862-1211
E-Mail: info@merz.com

EM00788-02/JAN 2016