RADIESSE®

INJECTABLE IMPLANT

INSTRUCTIONS FOR USE

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

DEVICE DESCRIPTION

RADIESSE is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE (1.3 cc and 0.3 cc) has a CaHA particle size range of 25-45 microns and should be injected with a 25 to 27 gauge needle.

INTENDED USE / INDICATIONS

RADIESSE is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds and it is also intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

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.

WARNINGS

- Use of RADIESSE 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 to RADIESSE have been observed consisting mainly of short-term (i.e., < 7 days) bruising, redness and swelling. Refer to adverse events sections for details.
- Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism.
- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of Radiesse occurs (see Patient Treatment).
- The safety and effectiveness of RADIESSE for use in the lips has not been established. There have been published reports of nodules associated with the use of RADIESSE injected into the lips.

PRECAUTIONS

- The calcium hydroxylapatite (CaHA) particles of RADIESSE are radiopaque and are clearly visible on CT Scans and may be visible in standard, plain radiography. Patients should be informed of the radiopaque nature of RADIESSE, 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 that RADIESSE potentially masked abnormal tissues or was interpreted as tumors in CT Scans.

- Radiesse should only be used by health care providers with expertise in the correction of volume deficiencies in patients with human immunodeficiency virus after fully familiarizing themselves with the product, the product educational materials and the entire package insert.

- RADIESSE 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.

- Long-term safety and effectiveness of RADIESSE beyond one year have not been investigated in clinical trials.

- The safety of RADIESSE in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied.

- As with all transcutaneous procecures, RADIESSE injection carries a risk of infection. Standard precautions associated with injectable materials should be followed.

- Safety of RADIESSE for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.

- 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.

- 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.

- 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.

- 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.

- Safety and effectiveness of RADIESSE in the periorbital area has not been established.

- No studies of interactions of RADIESSE with drugs or other substances or implants have been conducted.

ADVERSE EVENTS

A. NASOLABIAL FOLDS

Tables 1-4 contains the adverse events for 117 patients in a randomized, controlled study at 4 US investigational sites. Patients in the study received RADIESSE 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
Adverse Events
Reported Through Patient Diaries
Number of Patients With at Least One Adverse Event

By Adverse Event Type
N = 117

	RADIESSE	Control
	Total Reporting Symptoms N(%)	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)
Needle Jamming	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 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 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
Physician Reported Adverse Events
By Adverse Event Type

	RADIESSE	Control	RADIESSE				Control			
	Total Reporting Symptoms N(%)	Total Reporting Symptoms N(%)	Number of Days				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)
Needle Jamming	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)	17 (18.5)	8 (8.7)	12 (13.0)	8 (8.7)	10 (10.9)	11 (12.0)	11 (12.0)

Table 3
Physician Reported Adverse Events
Number of Patients With at Least One Adverse Event
By Adverse Event Type
N = 117

	RADIESSE	Control
	Total Reporting Symptoms N (%)	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 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

	RADIESSE	Control	RADIESSE				Control			
	Total Reporting Symptoms N(%)	Total Reporting Symptoms N(%)	Number of Days				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)

B. HIV-ASSOCIATED FACIAL LIPOATROPHY

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In a prospective, open label study of 100 patients at three U.S. sites, adverse events reported after RADIESSE treatments are provided in Tables 8-11. Adverse events reported in patient diaries during the 14 days after treatment are listed in Tables 5 and 6. 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 7 and 8.

Table 5
Number of Patients with Maximal Severity of Local Adverse Events Reported Through Patient Diaries
N = 100

Adverse Event	Patients Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Ecchymosis	64	34/64 (53.1)	25/64 (39.1)	5/64 (7.8)
Edema	99	46/99 (46.5)	49/99 (49.5)	4/99 (4.0)
Erythema	55	32/55 (58.2)	23/55 (41.8)	0/55 (0.0)
Granuloma	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Nodule	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Pain	37	24/37 (64.9)	13/37 (35.1)	0/37 (0.0)
Pruritis	21	18/21 (85.7)	3/21 (14.3)	0/21 (0.0)
Other*	43	27/43 (62.8)	15/43 (34.9)	1/43 (2.3)

* "Other" adverse events were those reported that did not fit into the categories detailed the tables above. The most common "Other" adverse event was contour irregularities. Additional "Other" adverse events included numbness, dryness, peeling, burning sensation, whiteheads and rash.

Table 6
Duration of Adverse Events as Reported Through Patient Diaries

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	142	29/142 (20.4%)	51/142 (35.9%)	50/142 (35.2%)	12/142 (8.5%)
Edema	430	205/430 (47.7%)	153/430 (35.6%)	52/430 (12.1%)	20/430 (4.7%)
Erythema	210	114/210 (54.3%)	69/210 (32.9%)	22/210 (10.5%)	5/210 (2.4%)
Pain	110	54/110 (49.1%)	32/110 (29.1%)	18/110 (16.4%)	6/110 (5.5%)
Pruritis	54	28/54 (51.9%)	9/54 (16.7%)	6/54 (11.1%)	11/54 (20.4%)
Other	112	40/112 (35.7%)	19/112 (17.0%)	18/112 (16.1%)	35/112 (31.3%)

Table 7
Maximal Severity of Local Adverse Events

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Physician Reported Adverse Events
N = 100

Adverse Event	Total Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Ecchymosis	3	2/3 (66.7)	1/3 (33.3)	0/3 (0.0)
Edema	8	8/8 (100.0)	0/8 (0.0)	0/8 (0.0)
Erythema	3	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)
Granuloma	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Nodule	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Pain	2	1/2 (50.0)	0/0 (0.0)	1/2 (50.0)
Pruritis	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Other*	26	20/26 (76.9)	6/26 (23.1)	0/26 (0.0)

* "Other" adverse events were those reported that did not fit into the categories detailed the tables above. The most common "Other" adverse event was contour irregularities. Additional "Other" adverse events included numbness, dryness, peeling, burning sensation, whiteheads and rash.

Table 8
Duration of Adverse Events
Physician Reported Adverse Events

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	5	3/5 (60.0%)	0/5 (0.0%)	2/5 (40.0%)	0/5 (0.0%)
Edema	13	10/13 (76.9%)	1/13 (7.7%)	1/13 (7.7%)	1/13 (7.7%)
Erythema	4	1/4 (25.0%)	2/4 (50.0%)	0/0 (0.0%)	1/4 (25.0%)
Pain	4	2/4 (50.0%)	0/4 (0.0%)	2/4 (50.0%)	0/4 (0.0%)
Pruritis	0	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
Other	62	27/62 (43.5%)	0/62 (0.0%)	1/62 (1.6%)	34/62 (54.8%)

CLINICAL STUDIES

A. NASOLABIAL FOLD CLINICAL DATA

Study design
The safety and effectiveness of RADIESSE for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. Patients were randomized to receive RADIESSE in one fold and a commercially available collagen implant in the contra-lateral 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 subjects 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 9.

Table 9
Patient Demographics, Nasolabial Folds
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%)

As indicated in Table 9, the study enrolled a population of predominantly female, Caucasian non-smokers.

Treatment Material Delivered

Volumes injected during the initial treatment phase are detailed in Table 10 below. The total mean volume for RADIESSE was 1.2mL and 2.4mL for the Control.

Table 10
Total Volume of Material Injected (mL), Nasolabial Folds
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 11 contains the mean LRS at baseline, 3 months and 6 months for the RADIESSE treated nasolabial folds and the Control treated nasolabial folds with the difference between the means. Baseline scores for the Radiesse and Control groups were not statistically different.

Table 11
Comparison of Mean LRS Scores* for RADIESSE and Control Nasolabial Folds - Baseline, 3 and 6 Months

	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 was non-inferior to Control for the correction of nasolabial folds 3 months after final treatment. At 3 months, 84.6% of the RADIESSE 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 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 treated nasolabial fold versus improvement on the Control treated nasolabial fold and that in at least 50% of patients, the RADIESSE treated nasolabial fold be superior to the Control treated nasolabial fold. At 6 months after optimal correction was achieved, 78.6% of the RADIESSE-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-treated nasolabial folds demonstrated superiority when compared to the mean LRS for the Control-treated nasolabial folds at 6 months ($p<0.0001$).

B. HIV-ASSOCIATED FACIAL LIPOATROPHY CLINICAL DATA

STUDY DESIGN

The safety and effectiveness of RADIESSE for the treatment of facial lipoatrophy was evaluated in a prospective, open-label, multi-center study of 100 patients with facial lipoatrophy with human immunodeficiency virus. Patients received an initial treatment (initial injection and an additional injection at 1 month as needed). Six months later, all patients were assessed for the need for a touch up injection. Effectiveness was assessed at 3, 6 and 12 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of adverse events through 12 months.

Study Endpoints
The primary endpoint of the study was to evaluate the correction of lipoatrophy 3 months after treatment by comparing changes from baseline on the GAIS. The GAIS is a 5-category scale (Very much improved, much improved, improved, no change and worse). The secondary endpoints of the study were to evaluate the correction of facial lipoatrophy 6 months after treatment by comparing changes from baseline on the GAIS, and 3 and 6 months after treatment by comparing changes from baseline in cheek skin thickness measurements.

Study Population
The inclusion criteria for the clinical study were that the patient was to be HIV positive, had a CD4 count ≥ 250 /mm^3 and viral load ≤ 5000 copies/mL, had been receiving HAART therapy for a minimum of 3 years, had HIV-associated facial lipoatrophy that was a grade 2, 3, or 4 on the Facial Lipoatrophy Severity Scale, was at least 18 years of age, signed a written informed consent, understood and accepted the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 12 month follow-up and understood and accepted the obligation and was logistically able to present for all scheduled follow-up visits

The exclusion criteria for the clinical study were patients that had a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease), had received or was anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre- to 1 month post-injection, was receiving systemic or topical corticosteroids or anabolic steroids, had another medical condition that would preclude study participation or suggested an AIDS diagnosis (e.g., Kaposi sarcoma, recurrent infection, recurrent pneumonia), had received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area, had received collagen in the cheek area within the past 6 months, had received over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study or intended to receive these products and/or treatments during the study, had facial hair that would preclude ability to assess facial lipoatrophy, had a history of keloid formation, was pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential and was enrolled in an interfering study.

Study Results
Demographics / Injection Information:

The study enrolled a population of predominantly multi-ethnic, non-smoking males (94% male) with a mean age of 48 years. Forty-four (44) percent of patients were Black, Hispanic or Asian. Fifty-six (56) percent were Caucasian. Fifty-one (51) percent of patients had a Fitzpatrick Skin score of IV, V or VI. All treatments were performed with a 25 gauge, 1½ inch needle. Mean initial treatment volumes were 4.8mL for the initial treatment and 1.8mL at 1 month if necessary (85% of patients were treated at 1 month). At 6 months, the mean touch up volume was 2.4mL (89% of patients). Four (4) percent of patients received only one treatment, 18% of patients received a total of two treatments and 78% of patients received a total of three treatments. No patient received more than three treatments.

Effectiveness Results:

A live GAIS rating was determined at 3 and 6 months (see Table 12).

Table 12
GAIS Ratings

% of Patients	3 Month N = 100	6 Month N = 98

Very Much Improved	26%	7%
Much Improved	72%	86%
Improved	2%	7%
No Change	0%	0%
Worse	0%	0%
Total	100%	100%

Cheek thickness measurements of patients left and right cheeks were performed at baseline, 3 and 6 months (see Table 13).

Table 13
Cheek Thickness Measurements

	BASELINE	3 MONTH			6 MONTH		
	Mean (N=100)	Mean (N=100)	Δ From Baseline	p-Value	Mean (N=97)	Δ From Baseline	p-Value
Left Cheek	4.7mm	7.3mm	2.6mm	<0.0001	7.1mm	2.4mm	<0.0001
Right Cheek	4.9mm	8.0mm	2.1mm	<0.0001	7.5mm	2.7mm	<0.0001

Patients provided responses to a 5-question patient satisfaction questionnaire at 3 and 6 months (see Table 14).

Table 14
Patient Satisfaction Assessment

	3 Months N = 100	6 Months N = 98
	Yes	Yes
Would you recommend RADIESSE treatment?	99%	99%
Has the RADIESSE treatment been beneficial to you?	100%	100%
Do you feel more attractive since receiving RADIESSE treatment?	98%	98%
Is your emotional wellbeing better since receiving RADIESSE?	91%	96%
Do you have more confidence in your appearance since receiving RADIESSE?	98%	98%

Short Term and Long Term Radiographic Evaluation of RADIESSE

RADIESSE contains calcium hydroxylapatite particles (25-45 microns) that are radiopaque and suspended in a water based gel. Therefore a radiographic study was conducted to assess the radiographic appearance of RADIESSE 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 of RADIESSE implanted.

A total of 58 patients in three patients groups were enrolled into the study. RADIESSE 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 RADIESSE, when in fact it was present. This may be due to the fact that the volume of RADIESSE in some patients was small and the sensitivity of X-ray imaging may not be sufficient to detect small volumes of RADIESSE. RADIESSE 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 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 for the CT Scan provided a superior image capability as compared to X-ray when visualizing Radiesse.

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 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 are required for the percutaneous injection procedure:

- RADIESSE syringe(s)
- 25-27 gauge needle 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. Local or topical anesthesia at the injection site should be used at the discretion of the physician.
2. Prepare the syringes of RADIESSE 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 cartor. 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. Remove the Luer syringe cap from the distal end of the syringe prior to attaching the needle. The syringe of RADIESSE can then be twisted onto the Luer lock fitting of the needle. **The needle must be tightened securely to the syringe and primed with RADIESSE.** If excess RADIESSE 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 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.
5. 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.
6. The amount injected will vary depending on the site and extent of the restoration or augmentation desired. RADIESSE should be injected subdermally.
7. Use a 1:1 correction factor. No overcorrection is needed.
8. 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.
9. 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. One needle jam occurred in the nasolabial fold clinical study. Needle jams are more likely with use of needles smaller than 27gauge.
10. Advance the needle into the subdermis to the starting location. Carefully push the plunger of the RADIESSE syringe to start the injection and slowly inject the RADIESSE material in linear threads while withdrawing the needle. Continue placing additional lines of material until the desired level of correction is achieved.
11. 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.

PATIENT COUNSELING INFORMATION

Refer to RADIESSE Patient Information Guide.

STORAGE

RADIESSE 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

BioForm Medical, Inc. warrants that reasonable care has been exercised in the design and manufacture of this product.

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A PATIENT'S GUIDE
RADIESSE® FOR THE RESTORATION AND/OR CORRECTION OF THE SIGNS OF FACIAL LOSS IN PEOPLE WITH HUMAN IMMUNODEFICIENCY VIRUS

(Calcium hydroxylapatite Microspheres in an aqueous gel carrier)

Read all the information before you are treated with Radiesse.

- Keep this information. You may need to read it again.
- If you have any questions, please ask your doctor.

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Introduction

This information will help you decide whether treatment with Radiesse is right for you. This information does not take the place of a discussion with your doctor but will answer some questions about treatment with Radiesse.

Please read this information and discuss any questions with your doctor. Only you and your doctor can decide whether Radiesse is right for you.

Glossary

Anesthetic:	A substance that causes loss of feeling or awareness. A topical or local anesthetic causes temporary loss of feeling in a part of the body, and may make your treatment more comfortable.
Facial Lipoatrophy:	The loss of facial fat.
Calcium hydroxylapatite	Calcium hydroxylapatite is a biocompatible, biodegradable material that is similar to one of the components commonly found in natural bone. Calcium hydroxylapatite has been widely used for many years in medical products.
Side effect:	An undesirable event caused by use of the product.

Background Information

What is Radiesse?

Radiesse is an injectable for treating facial fat loss associated with human immunodeficiency virus. Radiesse has a history of safe use in otology (ears), laryngeal (vocal chords), and dental and orthopedic applications.

Who might benefit from treatment with Radiesse?

Radiesse is intended for soft tissue augmentation and restoration of the face to correct facial lipoatrophy (lost facial fat).

Who should not use Radiesse?

Talk to your doctor about your medical history when deciding on treatment options. You should not use Radiesse if you are allergic to any ingredient of Radiesse. You may also not choose Radiesse if you desire only a short-term augmentation or restoration.

Are skin tests needed before treatment with Radiesse?

No skin testing is required prior to use.

How does Radiesse work?

Radiesse is injected below the surface of the skin in the area of fat loss. Radiesse results in aesthetic improvement and provides an increase in cheek thickness in the treated area. Visible results appear at the first treatment session. Radiesse will not correct the underlying cause of the facial lipoatrophy but will improve appearance in the treated area.

How many treatments are required?

Your doctor will decide with you the number of treatment sessions and the amount of Radiesse you will need at each treatment session. Generally, significant augmentation or restoration may be achieved in a first treatment. A touch-up may be required to achieve optimal results, and periodic future touch-up treatments may be needed to maintain the augmentation or restoration.

How often are treatments given?

Your doctor will decide how often treatments are given based upon your needs and desires and the areas and volume of treatment required.

How long do treatment effects last?

Treatment effects will differ for each person. In a clinical study, the treatment lasted for 1 year after the first treatment session in all patients.

Do injections of Radiesse hurt?

As with any injection, injections with Radiesse may hurt. Radiesse is injected in small amounts using a very fine needle. Your doctor may apply a topical or local anesthetic.

What can I expect to happen at a treatment session?

- Your doctor will answer all of your questions and prepare you for the treatment.
- The area where the injections will be given will be cleaned with an antiseptic.
- You and your doctor will determine if a topical or local anesthetic is needed.
- Radiesse will be injected in small amounts into the skin using a very fine needle.
- An ice pack may be applied to the treatment area before or after treatment to help reduce swelling.

What are the possible side effects of treatment with Radiesse?

Talk to your doctor about the possible side effects of Radiesse. The most common are redness, bruising, or swelling. These generally last for a short time and are mild in nature. As with all procedures that involve an injection through the skin, there is a risk of infection. However, no infections have been reported in the clinical study of Radiesse. Report any side effects you may experience to your doctor. The table below shows the side effects seen in a clinical study of 100 patients. Most of the side effects were seen at the time of the Radiesse injection, which is common for facial injection procedures (see Tables 1-4).

Table 1
Most Severe Side Effects
Reported Through Patient Diaries

Adverse Event	Total Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Bruising	64	34 (53.1)	25 (39.1)	5 (7.8)
Swelling	99	46 (46.5)	49 (49.5)	4 (4.0)
Redness	55	32 (58.2)	23 (41.8)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	37	24 (64.9)	13 (35.1)	0 (0.0)
Itching	21	18 (85.7)	3 (14.3)	0 (0.0)
Other	43	27 (62.8)	15 (34.9)	1 (2.3)

Table 2
Most Severe Side Effects
Reported Through Other Methods

Adverse Event	Total Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Bruising	3	2 (66.7)	1 (33.3)	0 (0.0)
Swelling	8	8 (100.0)	0 (0.0)	0 (0.0)
Redness	3	3 (100.0)	0 (0.0)	0 (0.0)
Granuloma	0	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0	0 (0.0)	0 (0.0)	0 (0.0)
Pain	2	1 (50.0)	0 (0.0)	1 (50.0)
Itching	0	0 (0.0)	0 (0.0)	0 (0.0)
Other	26	20 (76.9)	6 (23.1)	0 (0.0)

Table 3
Length of Time for Side Effects
Reported Through Patient Diaries

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Bruising	142	29 (20.4%)	51 (35.9%)	50 (35.2%)	12 (8.5%)
Swelling	430	205 (47.7%)	153 (35.6%)	52 (12.1%)	20 (4.7%)
Redness	210	114 (54.3%)	69 (32.9%)	22 (10.5%)	5 (2.4%)
Pain	110	54 (49.1%)	32 (29.1%)	18 (16.4%)	6 (5.5%)
Itching	54	28 (51.9%)	9 (16.7%)	6 (11.1%)	11 (20.4%)
Other	112	40 (35.7%)	19 (17.0%)	18 (16.1%)	35 (31.3%)

Table 4
Length of Time for Side Effects
Reported Through Other Methods

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Bruising	5	3 (60.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)
Swelling	13	10 (76.9%)	1 (7.7%)	1 (7.7%)	1 (7.7%)
Redness	4	1 (25.0%)	2 (50.0%)	0 (0.0%)	1 (25.0%)
Pain	4	2 (50.0%)	0 (0.0%)	2 (50.0%)	0 (0.0%)
Itching	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	62	27 (43.5%)	0 (0.0%)	1 (1.6%)	34 (54.8%)

Should I tell my doctor what medications I am taking?

Yes. You should tell your doctor about all the medicines you are taking, even over the counter medicines or treatments. If you are taking blood thinners or medications that may interfere with clotting of the blood, such as aspirin, you might be more likely to have bruising or bleeding at

the injection site. There have been no studies of possible interactions between Radiesse and drugs or other substances or implants. Talk to your doctor about your medical history when deciding on treatment options.

What can I expect after treatment?

Immediately following a treatment session with Radiesse redness, bruising or swelling may occur in the treatment area. These side effects usually go away in a short period and are generally mild in nature. An ice pack may be applied to the treatment area to help reduce swelling. Your doctor will give you specific post-treatment care instructions.
For approximately 24 hours after treatment:

- Avoid significant movement or massage of the treated area.
- Do not apply makeup.
- Avoid extensive sun or heat exposure

After you leave the office, you may experience redness, bruising or swelling for a few days. Not all patients experience these, but please remember that such side effects can occur and are not out of the ordinary for such a treatment.

You may be able to feel the area where Radiesse was injected for some period after injection. Over time, the injected area will feel more and more like your own tissue.

How quickly can I get back to my daily activities?

Most patients feel comfortable going back to their normal activities immediately after treatment with Radiesse.

What other things do I need to know?

The Microspheres in Radiesse can be seen in X-rays and CT Scans. It is very important that you inform your doctor and other health care professionals that you have Radiesse injected in your face. Even though Radiesse can be seen in X-rays and CT Scans, there is not a high risk that it would cause your doctor concern, as long as s/he knows that you have had Radiesse injected in your face.

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