Juvéderm

VOLUMA® XC

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

BEFORE USING PRODUCT, READ THE FOLLOWING INFORMATION THOROUGHLY.

1. DEVICE DESCRIPTION

JUVÉDERM VOLUMA® XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of crosslinked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 20 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

2. INTENDED USE/INDICATIONS

JUVÉDERM VOLUMA® XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face in adults over the age of 21.

3. CONTRAINDICATIONS

- JUVÉDERM VOLUMA® XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM VOLUMA® XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- JUVÉDERM VOLUMA® XC contains lidocaine and is contraindicated for patients with a history of allergies to such material.

4. WARNINGS

- The product must not be injected into blood vessels. Introduction of JUVÉDERM VOLUMA® XC into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers, for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage, leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur (see Health Care Professional Instructions #14).
- Product use at specific sites in which an active inflammatory process (skin eruptions such as cysts, pimples, rashes, or hives) or infection is present should be deferred until the underlying process has been controlled.
- Treatment site reactions consist mainly of short-term inflammatory symptoms and generally resolve within 2 to 4 weeks. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- JUVÉDERM VOLUMA® XC is packaged for single-patient use. Do not resterilize. Do not use if package is open or damaged.
- In order to minimize the risks of potential complications, this product 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.
- Health care professionals are encouraged to discuss all potential risks of soft tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
- Based on preclinical studies and a toxicological risk assessment, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (130 lbs) body mass per year. The safety of injecting greater amounts has not been established.
- The safety and effectiveness for the treatment of anatomic regions other than the mid-face have not been established in controlled clinical studies.
- As with all transcutaneous procedures, dermal filler implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- JUVÉDERM VOLUMA® XC is to be used as supplied. Modification or use of the product outside the Directions for Use may adversely impact the sterility, homogeneity, and performance of the product.
- The safety for use during pregnancy, in breastfeeding females, and in patients with very thin skin in the mid-face region has not been established.
- The safety for use in patients under 35 years or over 65 years has not been established.
- The safety in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- JUVÉDERM VOLUMA® XC should be used with caution in patients on immunosuppressive therapy.
- Patients who are using substances that can prolong bleeding (such as aspirin, nonsteroidal anti-inflammatory drugs, and warfarin) may, as with any injection, experience increased bruising or bleeding at treatment sites.
- Patients who experience skin injury near the site of JUVÉDERM VOLUMA® XC implantation may be at a higher risk for adverse events.
- Patients may experience late onset nodules with use of dermal fillers, including JUVÉDERM VOLUMA® XC. Refer to ADVERSE EVENTS section for details.
- After use, treatment syringes and needles may be potential biohazards. Handle and dispose of these items in accordance with accepted medical practice and applicable local, state, and federal requirements.
- JUVÉDERM VOLUMA® XC injectable gel is a clear, colorless gel without visible particulates. In the event that the content of a syringe shows signs of separation and/or appears cloudy, do not use the syringe; notify Allergan Product Surveillance at (877) 345-5372.
- JUVÉDERM VOLUMA® XC should only be used by health care professionals who have appropriate experience and who are knowledgeable about the anatomy and the product for use in deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation.
- Failure to comply with the needle attachment instructions could result in needle disengagement and/or product leakage at the LUER-LOK® and needle hub connection.

6. ADVERSE EVENTS

A. Clinical Evaluation of JUVÉDERM VOLUMA® XC

In the randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM VOLUMA® XC, there were 238 subjects treated with JUVÉDERM VOLUMA® XC in the mid-face (zygomaticomalar region, anteromedial cheek, and/or submalar region, see Figure 1) during the primary phase of the study. Touch-up treatments occurred approximately 30 days after initial injection. After the 6-month blinded "no treatment" control period, control subjects were allowed to receive treatment; 32 control subjects were treated in the study. Preprinted diary forms were used by subjects after treatment to record specific signs and symptoms experienced during each of the first 30 days after initial, touch-up, and repeat treatments in each region of the mid-face. Of the 270 subjects who underwent treatment (from both the treatment and control groups), 265 completed the diary forms. A subset of subjects also underwent repeat treatment following completion of the extended follow-up phase of the study, with 162 subjects completing diary forms after repeat treatment. Subjects were instructed to rate each treatment site response listed on the diary as "Mild (barely noticeable)," "Moderate (uncomfortable)," "Severe (severe discomfort)," or "None."

After initial treatment with JUVÉDERM VOLUMA® XC, 98% of subjects reported experiencing a local treatment site response. Subjects rated treatment site responses as predominantly mild (21.5%) or moderate (59.2%) in severity with a duration of 2 to 4 weeks. For those treatment site responses evaluated as moderate or severe, the median duration as moderate or severe was 2 days, and the median time to complete resolution was 6 days. Based on data from 167 subjects who received repeat treatment, treatment site responses following repeat treatment were less severe, with reduced incidence and duration compared to initial treatment.

Treatment site responses reported by > 5% of subjects after initial treatments are summarized by severity in Table 1 and by duration in Table 2.

Table 1: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects After Initial Treatment (N = 265)

	Severity[a]			
Treatment Site Response	**Total**	**Mild**	**Moderate**	**Severe**
	% (n/N[b])	**% (n/N)**	**% (n/N)**	**% (n/N)**
Any Treatment Site Response	98.1% (260/265)	21.5% (56/260)	59.2% (154/260)	19.2% (50/260)
Tenderness	92.1% (244/265)	46.3% (113/244)	50.0% (122/244)	3.7% (9/244)
Swelling	85.7% (227/265)	46.7% (106/227)	43.6% (99/227)	9.7% (22/227)
Firmness	82.3% (218/265)	37.6% (82/218)	54.6% (119/218)	7.8% (17/218)
Lumps/Bumps	81.1% (215/265)	41.4% (89/215)	48.8% (105/215)	9.8% (21/215)
Bruising	77.7% (206/265)	37.4% (77/206)	51.5% (106/206)	11.2% (23/206)
Pain	66.4% (176/265)	59.1% (104/176)	38.6% (68/176)	2.3% (4/176)
Redness	66.0% (175/265)	60.0% (105/175)	36.0% (63/175)	4.0% (7/175)
Discoloration	41.1% (109/265)	62.4% (68/109)	27.5% (30/109)	10.1% (11/109)
Itching	38.5% (102/265)	70.6% (72/102)	18.6% (19/102)	10.8% (11/102)

[a] Maximum severity reported in the diary. The denominator for percentages by severity is the number of subjects with the corresponding treatment site response.

[b] N denotes number of subjects who recorded responses in the diaries after the initial treatment.

Treatment site responses reported by ≤ 5% of subjects included ache, acne, bulge, bumps, cheek larger upon waking up, dry patch, fine wrinkles, injection/needle marks, numbness, pigmentation from treatment, puffiness, rash, scratch near injection point, soreness, tightness, and yellowness.

Table 2: Duration of Treatment Site Responses After Initial Treatment (N = 265)

	Duration[a]					
Treatment Site Response	**Total**	**1-3 Days**	**4-7 Days**	**8-14 Days**	**15-30 Days**	**> 30 Days**
	% (n/N[b])	**% (n/N)**	**% (n/N)**	**% (n/N)**	**% (n/N)**	**% (n/N)**
Any Treatment Site Response	98.1% (260/265)	8.1% (21/260)	22.7% (59/260)	24.6% (64/260)	24.6% (64/260)	20.0% (52/260)
Tenderness	92.1% (244/265)	29.9% (73/244)	30.7% (75/244)	27.9% (68/244)	8.6% (21/244)	2.9% (7/244)
Swelling	85.7% (227/265)	41.0% (93/227)	33.0% (75/227)	17.6% (40/227)	5.3% (12/227)	3.1% (7/227)
Firmness	82.3% (218/265)	26.6% (58/218)	29.8% (65/218)	20.2% (44/218)	11.0% (24/218)	12.4% (27/218)
Lumps/Bumps	81.1% (215/265)	21.4% (46/215)	22.3% (48/215)	22.3% (48/215)	18.1% (39/215)	15.8% (34/215)
Bruising	77.7% (206/265)	24.8% (51/206)	30.6% (63/206)	29.6% (61/206)	14.6% (30/206)	0.5% (1/206)
Pain	66.4% (176/265)	56.3% (99/176)	31.3% (55/176)	9.7% (17/176)	2.8% (5/176)	0% (0/176)
Redness	66.0% (175/265)	59.4% (104/175)	28.0% (49/175)	8.6% (15/175)	2.3% (4/175)	1.7% (3/175)
Discoloration	41.1% (109/265)	64.2% (70/109)	19.3% (21/109)	6.4% (7/109)	5.5% (6/109)	4.6% (5/109)
Itching	38.5% (102/265)	81.4% (83/102)	16.7% (17/102)	2.0% (2/102)	0% (0/102)	0% (0/102)

[a] Maximum duration reported in the diary. The denominator for percentages by duration is the number of subjects with the corresponding treatment site response.

[b] N denotes number of subjects who recorded responses in the diaries after the initial treatment.

Treatment site responses reported in subject diaries that lasted longer than 30 days were considered adverse events (AEs). AEs were also reported by the Treating Investigator at all follow-up visits where applicable. Table 3 summarizes device/injection-related AEs that occurred with a frequency of > 1%. These adverse events were seen more frequently in subjects that received injection volumes greater than 9 mL and in older subjects (> 60 years). Rarely, adverse events occurred weeks to months after the injection procedure.

Among the 270 treated subjects, 32.6% (88/270) experienced device/injection-related AEs following initial and touch-up treatment, 99% (624/627) of which were reported at a treatment site. The treatment site AEs were evenly divided across the 3 mid-facial regions. Fewer AEs occurred after repeat treatment than after initial/touch-up treatment.

Table 3: Device/Injection-Related Adverse Events Occurring in > 1% of Treated Subjects (N = 270)

Adverse Event	Treated Subjects % (n/N)
Treatment site mass	18.9% (51/270)
Treatment site induration	14.1% (38/270)
Treatment site swelling	7.0% (19/270)
Treatment site pain	5.9% (16/270)
Treatment site hematoma	3.7% (10/270)
Treatment site discoloration	2.2% (6/270)
Treatment site erythema	1.9% (5/270)
Treatment site reaction	1.5% (4/270)

Device/injection-related adverse events occurring in ≤ 1% of subjects included injection site hypertrophy (0.7%), nodule (0.7%), inflammation (0.4%), injection site anesthesia (0.4%), injection site dryness (0.4%), injection site erosion (0.4%), mass (0.4%), contusion (0.4%) and syncope (0.4%).

Two subjects (0.7%; 2/270) reported 3 serious adverse events (SAEs) that were considered to be related to the device. Approximately 6 months after treatment, after being scratched near the treated area by a tree branch, one subject experienced inflammation under the left eye. The subject also experienced nodularity in the right cheek approximately 7 months after treatment. The second subject experienced lumps in the cheeks approximately 7 months after treatment. A couple of days before the onset, the subject experienced myofascial pain and body aches. Treatment of the SAEs included topical steroids, oral antibiotics, intralesional steroids, anti-inflammatory medication, and hyaluronidase. All events resolved.

B. 1-Year Post-Approval Study of JUVÉDERM VOLUMA® XC

The post-approval study was a statistical evaluation of safety data collected in the JUVÉDERM VOLUMA® XC pivotal study. Safety data were analyzed from subjects who elected to undergo repeat treatment with JUVÉDERM VOLUMA® XC as part of the pivotal study. Pre-printed diary forms were used by subjects to record specific signs and symptoms experienced during each of the first 30 days after repeat treatment.

Treatment site responses reported by subjects in their diaries after repeat treatment are summarized by severity in Table 4 and by duration in Table 5. The incidence of treatment site responses after repeat treatment was lower than the incidence after initial/touch-up treatment, and treatment site responses were generally less severe and shorter in duration after repeat treatment compared to initial/touch-up treatment. The majority of treatment site responses after repeat treatment resolved within 2 weeks, while treatment site responses after initial/touch-up treatment typically resolved within 2 to 4 weeks.

Table 4: Treatment Site Responses by Maximum Severity Occurring in > 5% of Subjects After Repeat Treatment (N = 167)

Treatment Site Response	Severity[a]			
	Total	Mild	Moderate	Severe
	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])
Any Treatment Site Response	90.1% (146/162)	30.8% (45/146)	54.8% (80/146)	14.4% (21/146)
Tenderness	76.5% (124/162)	52.4% (65/124)	42.7% (53/124)	4.8% (6/124)
Swelling	67.9% (110/162)	42.7% (47/110)	54.5% (60/110)	2.7% (3/110)
Firmness	66.0% (107/162)	40.2% (43/107)	57.0% (61/107)	2.8% (3/107)
Bruising	62.3% (101/162)	49.5% (50/101)	37.6% (38/101)	12.9% (12/101)
Lumps/Bumps	58.0% (94/162)	46.8% (44/94)	47.9% (35/94)	5.3% (5/94)
Redness	56.8% (92/162)	59.8% (55/92)	38.0% (35/92)	2.2% (2/92)
Pain	54.9% (89/162)	65.2% (58/89)	30.3% (27/89)	4.5% (4/89)
Itching	32.7% (53/162)	79.2% (42/53)	20.8% (11/53)	0% (0/53)
Discoloration	26.5% (43/162)	72.1% (31/43)	27.9% (12/43)	0% (0/43)

[a] Maximum severity reported in the diary. The denominator for percentages by severity is the number of subjects with corresponding treatment site response.

[b] N denotes number of subjects who recorded responses in the diaries after the repeat treatment.

Table 5: Duration of Treatment Site Responses After Repeat Treatment (N = 167)

Treatment Site Response	Duration[a]					
	Total	1-3 Days	4-7 Days	8-14 Days	15-30 Days	> 30 Days
	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])	% (n/N[b])
Any Treatment Site Response	90.1% (146/162)	18.5% (27/146)	30.1% (44/146)	24.0% (35/146)	19.2% (28/146)	8.2% (12/146)
Tenderness	76.5% (124/162)	42.7% (53/124)	32.3% (40/124)	13.7% (17/124)	10.5% (13/124)	0.8% (1/124)
Swelling	67.9% (110/162)	61.8% (68/110)	23.6% (26/110)	7.3% (8/110)	6.4% (7/110)	0.9% (1/110)
Firmness	66.0% (107/162)	26.2% (28/107)	33.6% (36/107)	19.6% (21/107)	14.0% (15/107)	6.5% (7/107)
Bruising	62.3% (101/162)	33.7% (34/101)	33.7% (34/101)	23.8% (24/101)	7.9% (8/101)	1.0% (1/101)
Lumps/Bumps	58.0% (94/162)	37.2% (35/94)	28.7% (27/94)	16.0% (15/94)	10.6% (10/94)	7.4% (7/94)
Redness	56.8% (92/162)	58.7% (54/92)	29.3% (27/92)	7.6% (7/92)	4.3% (4/92)	0% (0/92)
Pain	54.9% (89/162)	65.2% (58/89)	20.2% (18/89)	11.2% (10/89)	3.4% (3/89)	0% (0/89)
Itching	32.7% (53/162)	81.1% (43/53)	13.2% (7/53)	5.7% (3/53)	0% (0/53)	0% (0/53)
Discoloration	26.5% (43/162)	76.7% (33/43)	7.0% (3/43)	7.0% (3/43)	7.0% (3/43)	2.3% (1/43)

[a] Maximum duration reported in the diary. The denominator for percentages by duration is the number of subjects with corresponding treatment site response.

[b] N denotes number of subjects who recorded responses in the diaries after the repeat treatment.

Among the 167 subjects who received repeat treatment, 8.4% (14/167) experienced a device/injection-related AEs following treatment. All AEs after repeat treatment occurred within 1 month of repeat treatment. The rate of device/injection-related AEs was lower after repeat treatment compared to initial/touch-up treatment. The most common AEs were injection site mass and induration (Table 6).

Table 6: Device/Injection-Related AEs After Repeat Treatment Occurring in > 1% of Treated Subjects (N = 167)

Adverse Event	Treated Subjects % (n/N)
Injection Site Mass	4.2% (7/167)
Injection Site Induration	4.2% (7/167)
Injection Site Bruising	1.2% (2/167)

All device/injection-related AEs after repeat treatment were mild to moderate, required no action, and resolved without sequelae. Generally, device/injection-related AEs were less severe after repeat treatment compared to initial/touch-up treatment, and most resolved within 3 months. Similar to the initial/touch-up treatment, 3 subjects experienced a device/injection-related AE that lasted more than 180 days, but all resolved without requiring any treatment. Device/injection-related adverse events occurring in ≤ 1% of subjects included injection site swelling (0.6%), injection site pain (0.6%), and injection site papule (0.6%).

Of the 121 subjects who completed the 12 months of follow-up after repeat treatment, none experienced any late onset device/injection-related AEs (those occurring more than 1 month after repeat treatment). There were no device/injection-related serious adverse events after repeat treatment.

C. Other Safety Data

Postmarket Surveillance

JUVÉDERM VOLUMA® without lidocaine has been marketed outside the US since 2005, and JUVÉDERM VOLUMA® XC (also known as JUVÉDERM VOLUMA® with lidocaine) has been marketed outside the US since 2009 and in the US since 2013.

The following AEs were received from postmarket surveillance for JUVÉDERM VOLUMA® with and without lidocaine with a frequency of 5 events or more and were not observed in the clinical study; this includes reports received globally from all sources including scientific journals and voluntary reports. All AEs obtained through postmarket surveillance are listed in order of number of reports received: inflammatory reaction, lack of correction, infection, migration, allergic reaction, abscess, paresthesia, vascular occlusion, drainage, necrosis, vision abnormalities, malaise, scarring, nausea, granuloma, deeper wrinkle, and dyspnea. Reported treatments include: antibiotics, steroids, antiseptic creams, hyaluronidase, anti-inflammatories, antihistamines, needle aspiration, eye drops, radio frequency therapy, hyperbaric oxygen treatment, laser treatment, ice, massage, warm compress, analgesics, anti-virals, ultrasound therapy, excision, drainage, and surgery.

Vision abnormalities have been reported following injection of JUVÉDERM VOLUMA®, with and without lidocaine, into the nose, glabella, periorbital area, and/or cheek, with a time to onset ranging from immediate to 1 week following injection. Reported treatments include anticoagulants, sympathomimetics, steroids, and surgery. Outcomes ranged from resolved to ongoing at the time of last contact. Events requiring medical intervention, and events where resolution information is not available, were reported after injection of JUVÉDERM VOLUMA® with and without lidocaine in the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (see Warnings section).

Adverse reactions should be reported to Allergan Product Surveillance Department at (877) 345-5372.

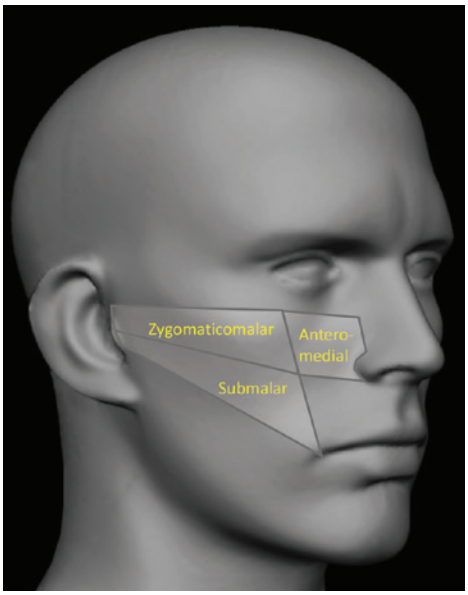
7. CLINICAL STUDIES

A. Pivotal Study for JUVÉDERM VOLUMA® XC

Pivotal Study Design

A multi-center, single-blind, randomized, no-treatment controlled pivotal clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM VOLUMA® XC for cheek augmentation to correct age-related volume deficit in the mid-face. Subjects were randomized to treatment or no-treatment control in a 5.3:1 ratio. Treatment group subjects underwent treatment with JUVÉDERM VOLUMA® XC at the outset of the study. Up to 2 treatments approximately 1 month apart (initial treatment and up to 1 touch-up treatment) were allowed. The Treating Investigator determined the appropriate volume of JUVÉDERM VOLUMA® XC to be injected in the 3 sub-regions of the mid-face: zygomaticomalar region, anteromedial cheek region, and submalar region, which are depicted in Figure 1. Treatment of the nasolabial folds and periorbital region was prohibited. The no-treatment control subjects had treatment delayed for 6 months.

Figure 1. Mid-Face Regions Treated



Treated subjects returned for routine safety visits with the Treating Investigator at 1, 3, and 6 months after the last treatment during the primary safety and effectiveness phase. All subjects returned for effectiveness follow-up visits with 2 independent Evaluating Investigators (EI) at 1, 3, and 6 months after the last treatment. EIs assessed subjects' overall mid-face volume deficit on the validated 6-point photometric Mid-Face Volume Deficit Scale (MFVDS) as well as volume deficit for each of the 3 facial sub-regions. EIs also assessed subjects' improvement on the 5-point Global Aesthetic Improvement Scale (GAIS), the 5-point photometric Nasolabial Fold Photo Severity Scale (NLFSS), and the 11-point Other Aesthetic Features of the Mid-Face questionnaire. Subjects performed self-assessments on MFVDS, GAIS, NLFSS, treatment goal achievement, satisfaction with mid-facial regions, self-perception of age, look and feel of the face, and satisfaction with facial appearance. Further, 3D facial photography was performed, and volume changes were calculated.

During the extended follow-up period, subjects returned for safety and effectiveness evaluations at quarterly intervals up to 24 months or until any visit at or after Month 12 when the average of the EIs' live assessments of the MFVDS returned to, or was worse than, the pre-treatment level. Control subjects followed a similar effectiveness evaluation schedule through Month 6 but were not treated and not required to undergo safety evaluations or self-assessments of effectiveness. After Month 6, control subjects received treatment and followed the same treatment and follow-up schedule as the treatment group. An optional repeat treatment was offered to all subjects after completion of the extended follow-up period, with continued follow-up through 12 months after repeat treatment.

Study Endpoints

The primary effectiveness measure was the average of the 2 blinded EIs' live assessments of the subject's overall mid-face volume deficit on the validated 6-point photometric MFVDS. A responder was defined as a subject with ≥ 1 grade improvement in the average MFVDS score since baseline. Effectiveness of JUVÉDERM VOLUMA® XC was demonstrated if at least 70% of subjects treated with JUVÉDERM VOLUMA® XC were responders at Month 6, and if the responder rate for the treatment group was statistically superior to that of the no-treatment control group at Month 6.

Secondary measures included the level of improvement on the GAIS and MFVDS assessments for each region of the mid-face as assessed by the blinded EIs.

Subject Demographics

A total of 345 subjects were enrolled in the study: 16 were screen failures primarily due to ineligibility, 30 were run-in subjects, and 299 were randomized per protocol, 17 of whom discontinued prior to treatment. Of the remaining 282 subjects, 235 were randomized to the treatment group, and 47 were randomized to the control group. Three-fourths (74.0%, 174/235) of the treatment group completed the extended follow-up period. Sixty-one subjects (26.0%, 61/235) discontinued the study primarily due to loss to follow-up (34.4%, 21/61) or withdrawal of consent (36.1%, 22/61).

At baseline, the majority of subjects in the treatment group (93.6%, 220/235) and all subjects in the control group (100%, 46/46) had moderate, significant, or severe volume deficit (encompassing scores of 2.5 through 5 on the MFVDS scale) in their mid-face according to the average of EI assessments. Subject demographics and pre-treatment characteristics are presented in Table 7.

Table 7: Demographics and Pre-treatment Characteristics (N = 282)

		Treatment Group	Control Group
		(N = 235)	(N = 47)
Characteristic		% (n)	% (n)
Gender	Female	80% (189)	79% (37)
	Male	20% (46)	21% (10)
Age (years)	Median	56	55
	Range (min, max)	(35-65)	(36-65)
Race	Caucasian	58% (137)	60% (28)
	Hispanic	15% (35)	9% (4)
	African-American	19% (44)	26% (12)
	Asian	4% (9)	6% (3)
	Other	4% (10)	0% (0)
Fitzpatrick Skin Type	I	3% (6)	4% (2)
	II	26% (62)	21% (10)
	III	29% (67)	23% (11)
	IV	18% (43)	30% (14)
	V	19% (44)	19% (9)
	VI	6% (13)	2% (1)

Treatment Characteristics

Multiple injection techniques were used for 95% of subjects, with the most common being tunneling, fanning, and serial puncture. Subjects were injected equally in the 3 facial sub-regions for a total median volume of 2.0 mL for the zygomaticomalar region, 2.0 mL for the anteromedial cheek, and 2.1 mL for the submalar region. The overall total volume used to achieve optimal correction for all 3 sub-regions ranged from 1.2 mL to 13.9 mL, with a median of 6.6 mL. The median volume at initial treatment was 4.8 mL. A touch-up treatment was performed for 82% (195/238) of subjects. The median total volume used for touch-up treatment was 1.9 mL. The median volume injected for repeat treatment was 2.0 mL. The volume of JUVÉDERM VOLUMA® XC varied depending on the subject's volume deficit and treatment goal.

Primary Effectiveness Results

JUVÉDERM VOLUMA® XC provided a clinically and statistically significant improvement in mid-face volume deficit compared to the no-treatment control group. Primary effectiveness was met in that significantly greater than 70% of subjects in the treatment group were responders (85.6% improved by ≥ 1 grade compared with their pre-treatment assessment, $p < 0.0001$ against the 70% responder rate threshold), and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (a difference of 46.7%) at Month 6 (Table 8). JUVÉDERM VOLUMA® XC was found to be effective in all Fitzpatrick skin phototypes, for males and females, and across the studied age range.

Table 8: Effectiveness Summary Responder Rate at 6 Months Based on Evaluating Investigators' Assessments

	Responder Rate at Month 6	p-value
Treatment Group	85.6% (178/208)	< 0.0001
Control Group[a]	38.9% (14/36)	
Difference in Responder Rates (Treatment rate - Control rate)	46.7%	< 0.0001

[a] Includes 2 subjects who were treated in error.

Secondary Effectiveness Results

The GAIS responder rate for the treatment group was 82.2% (171/208) at Month 6, where the responder rate was the percent of subjects with a score of ≥ 1 (improved or much improved) on the GAIS for overall mid-face volume based on EIs' assessments. At Month 6 the MFVDS responder rate for each of the facial sub-regions was above 75%.

Extended Follow-Up

Table 9 shows the mean MFVDS scores during the extended follow-up period (Months 9 to 24). The mean improvement was clinically significant (≥ 1 point), with the majority of subjects demonstrating improvement.

- 86.6% (181/209) at Month 9
- 85.2% (172/203) at Month 12
- 71.5% (128/179) at Month 18
- 67.1% (112/167) at Month 24

Table 9: Mean MFVDS Scores After Initial/Touch-Up Treatment

Visit	N	Mean MFVDS Score	Mean Change Since Baseline
Baseline	235	3.3	N/A
Month 9	209	1.7	1.6
Month 12	203	1.8	1.5
Month 18	179	2.1	1.3
Month 24	167	2.2	1.1

Subject Self-Assessments

Subjects performed numerous self-assessments, including satisfaction with facial appearance, self-perception of age, and NLF severity. At each time point, more than three-fourths of the treatment group subjects demonstrated an improvement in the overall satisfaction with facial appearance since baseline. In addition, the majority of treatment group subjects perceived themselves as looking younger than at baseline, from 76.4% at Month 1 to 55.4% at Month 24. Subjects, on average, reported themselves as looking approximately 5 years younger at Month 6 and 3 years younger at Month 24. Lastly, more than half (57%, 236/414) of the treatment group subjects at Month 6 observed a ≥ 1-point improvement in their NLFs.

B. Post-Approval Study for JUVÉDERM VOLUMA® XC

Post-Approval Study Design

The post-approval study was a statistical evaluation of safety data collected from the pivotal study for JUVÉDERM VOLUMA® XC. The safety data were analyzed for subjects who elected to undergo repeat treatment with JUVÉDERM VOLUMA® XC as part of the pivotal study. Treated subjects returned for safety visits with the Treating Investigator at 1, 3, 6, 9, and 12 or 12+ months. There were 14 enrolled study sites and 167 subjects from the pivotal study who received repeat treatment and were included in the post-approval study.

The study objective was to compare device/injection-related AEs before and after repeat treatment for subjects who received both initial/touch-up and repeat treatments.

Subject Accountability

After repeat treatment, 93.4% of subjects (156/167) attended the Month 1 visit. Of the 167 subjects, 127 subjects consented to long-term follow-up. At the end of the study, 95.3% of subjects (121/127) completed the follow-up at 12 or 12+ months.

Subject Demographics

Subject demographics (gender, age, race/ethnicity, and Fitzpatrick skin type) for the 167 subjects who received repeat treatment are shown in Table 10. The majority of subjects were female and Caucasian, with a median age of 56. Subjects were distributed across all Fitzpatrick Skin Types, with the majority being Fitzpatrick II, III, and IV.

Table 10: Post-Approval Study Subject Demographics

		% (n/N)
Characteristic		**(N = 167)**
Gender	Female	77.8% (130/167)
	Male	22.2% (37/167)
Age (years)	Mean	54.8
	Standard Deviation	6.70
	Median	56.0
	Range (min, max)	(37, 65)
Race	Caucasian	64.1% (107/167)
	Hispanic	10.8% (18/167)
	African-American	16.2% (27/167)
	Asian	3.6% (6/167)
	Other	5.4% (9/167)
Fitzpatrick Skin Type	I	3.6% (6/167)
	II	27.5% (46/167)
	III	28.1% (47/167)
	IV	21.0% (35/167)
	V	15.6% (26/167)
	VI	4.2% (7/167)

Study Safety Findings

The primary endpoint was met, demonstrating that the safety profile of JUVÉDERM VOLUMA® XC after repeat treatment was not worse than the safety profile after initial/touch-up treatment. The rate of AEs after repeat treatment [8.4% (14/167)] was significantly lower than the rate of AEs after initial/touch-up treatment [33.5% (56/167)].

No new safety concerns were identified after repeat treatment. The types of treatment site responses and AEs observed after repeat treatment were similar to those after initial/touch-up treatment, but were generally less severe after repeat treatment. Most treatment site responses after repeat treatment were mild to moderate and resolved within 2 weeks. Device/injection-related AEs after repeat treatment were all mild to moderate, required no action, and resolved without sequelae, with most resolving within 3 months. After repeat treatment, no subjects experienced any late onset device/injection-related AEs (those occurring more than 1 month after repeat treatment) and no device/injection-related SAEs occurred.

The results of a multivariate analysis demonstrated that device/injection-related AE rates were different among clinical sites, increased with higher injection volumes, and were higher in females as compared to males.

Study Strengths/Limitations

The strength of the study is that long-term safety data were collected after repeat treatment, with high subject compliance (95.3%) at the end of the study (12/12+ month visit). A limitation of the study was that the length of follow-up after repeat treatment was approximately one year shorter than after initial/touch-up treatment.

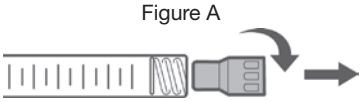
8. INSTRUCTIONS FOR USE

A. To Attach Needle to Syringe

STEP 1: Remove tip cap

Hold syringe and pull tip cap off the syringe, as shown in Figure A.

Figure A



STEP 2: Insert needle

Hold the syringe body and firmly insert the hub of the needle (provided in the JUVÉDERM VOLUMA® XC package) into the LUER-LOK® end of the syringe.

STEP 3: Tighten the needle

Tighten the needle by turning it firmly in a clockwise direction (see Figure B) until it is seated in the proper position, as shown in Figure C.

NOTE: If the position of the needle cap is as shown in Figure D, it is not attached correctly. Continue to tighten until the needle is seated in the proper position.

Figure B

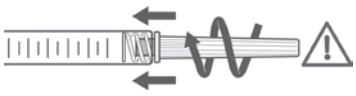


Figure C

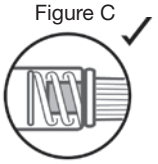


Figure D

STEP 4: Remove the needle cap

Hold the syringe body in one hand and the needle cap in the other. Without twisting, pull in opposite directions to remove the needle cap, as shown in Figure E.

Figure E

B. Health Care Professional Instructions

1. JUVÉDERM VOLUMA® XC injectable gel is a crosslinked, robust, injectable gel formulation, injected using a 27G ½" or 25G 1" needle to volumize and contour the cheek for correction of mid-face volume deficit.
2. Prior to treatment, the patient's medical history should be obtained, and the patient should be fully apprised of the indications, contraindications, warnings, precautions, treatment responses, adverse reactions, and method of administration. Patients also should be advised that supplemental "touch-up" implantations may be required to achieve and maintain maximum correction.
3. The patient's soft-tissue deficiencies should be characterized with regard to etiology, distensibility, stress at the site, and depth of lesion. Pre-treatment photographs are recommended.
4. Topical or injectable anesthesia may be used to manage pain during and after injection.
5. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be prepped with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle.
6. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
7. After insertion of the needle, and just before injection, the plunger rod should be withdrawn slightly to aspirate and verify the needle is not intravascular.
8. After the first small amount of material has been injected into the patient, wait a full 3 seconds to allow the lidocaine to take effect before proceeding with the rest of the injection.
9. The injection technique for JUVÉDERM VOLUMA® XC with regard to the angle and orientation of the bevel, the depth (subcutaneous and/or submuscular/supraperiosteal) of injection, and the quantity administered may vary depending on the area being treated. Injection of JUVÉDERM VOLUMA® XC too superficially (intradermally), or in large volumes over a small area, may result in visible and persistent lumps and/or discoloration.
10. Tunneling, fanning, serial puncture, crosshatching, and ferning techniques may be used with JUVÉDERM VOLUMA® XC to achieve optimal results. Injection may be administered in an antegrade or retrograde fashion. Inject JUVÉDERM VOLUMA® XC while applying even pressure on the plunger rod and slowly moving the needle in the subcutaneous or submuscular/supraperiosteal plane.
11. JUVÉDERM VOLUMA® XC should be distributed in small aliquots (small boluses of 0.1 mL to 0.2 mL) over a large area to reduce the risk of persistent lumpiness.
12. With submuscular/supraperiosteal injection, the number of times the needle passes through the muscle should be minimized to reduce the risk of bruising. It is important to stop injecting before the needle tip reaches the level of the deep dermis to prevent material from being placed too superficially in the skin.

13. Correct to 100% of the desired volume effect. Do not overcorrect. The degree and duration of the correction depend on the character of the defect treated, the tissue stress at the implant site, the depth of the implant in the tissue, and the injection technique. Markedly indurated defects may be difficult to correct.
14. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color. Blanching may represent a vessel occlusion. If normal skin coloring does not return, do not continue with the injection. Treat in accordance with American Society for Dermatologic Surgery guidelines, which include hyaluronidase injection.[1]
15. The area of lost facial volume should be lifted by the end of the injection. When injection is completed, the treated site may be gently massaged to mold the product to the contour of the surrounding tissue and assure that it is evenly distributed and conforms to the contour of the surrounding tissues. If overcorrection occurs, massage the area between your fingers or against an underlying superficial bone to obtain optimal results.
16. With patients who have localized swelling, the degree of correction is sometimes difficult to judge at the time of treatment. In these cases, it is better to invite the patient back to the office for a touch-up treatment.
17. After the initial treatment, an additional treatment may be necessary to achieve the desired level of correction. The same procedure should be repeated until a satisfactory result is obtained. The need for an additional treatment may vary from patient to patient and is dependent upon a variety of factors such as mid-face volume deficit severity, skin elasticity, and dermal thickness at the treatment site.
18. Patients may experience treatment site responses, which typically resolve within 2 to 4 weeks. Ice may be applied for a brief period following treatment to minimize swelling and reduce pain.
19. The health care professional should instruct the patient to promptly report any evidence of problems possibly associated with the use of JUVÉDERM VOLUMA® XC.

C. Patient Instructions

It is recommended that the following information be shared with patients:

- Within the first 24 hours, patients should avoid strenuous exercise and extensive sun or heat exposure. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the treatment sites
- If the treated area is swollen, an ice pack may be applied to the site for a short period
- To report an adverse reaction, phone the Allergan Product Surveillance Department at (877) 345-5372

9. HOW SUPPLIED

JUVÉDERM VOLUMA® XC injectable gel is supplied in individual treatment syringes with needles as indicated on the carton. JUVÉDERM VOLUMA® XC can be injected with either a 27G ½" or a 25G 1" needle. The volume in each syringe is as stated on the syringe label and on the carton. The contents of the syringe are sterile and non-pyrogenic. Do not resterilize. Do not use if package is open or damaged.

10. SHELF LIFE AND STORAGE

JUVÉDERM VOLUMA® XC injectable gel must be used prior to the expiration date printed on the label.

Store at room temperature (up to 25°C/77°F). DO NOT FREEZE.

JUVÉDERM VOLUMA® XC injectable gel has a clear appearance. In the event that a syringe contains material that is not clear, do not use the syringe; notify Allergan Product Surveillance immediately at (877) 345-5372.

To place an order, contact Allergan at (800) 377-7790.

[1]Alam M, Gladstone H, Kramer EM, et al. ASDS guidelines of care: injectable fillers. *Dermatol Surg*. 2008;34(suppl 1):S115-S148.

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