JUVÉDERM®
ULTRA 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® Ultra XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked hyaluronic acid (HA) produced by *Streptococcus* species of bacteria, formulated to a concentration of 24 mg/mL and 0.3% w/w lidocaine in a physiologic buffer.

2. INTENDED USE/INDICATIONS

- JUVÉDERM® Ultra XC injectable gel is indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).
- JUVÉDERM® Ultra XC is indicated for injection into the lips and perioral area for lip augmentation in adults over the age of 21.

3. CONTRAINDICATIONS

- JUVÉDERM® Ultra XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM® Ultra XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
- JUVÉDERM® Ultra 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® Ultra 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soft-tissue fillers; for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary.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 professional specialist should an intravascular injection occur (see Health Care Professional Instructions #13).
- 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.
- Injection site reactions consist mainly of short-term inflammatory symptoms starting early after treatment and lasting ≤ 7 days in facial wrinkles and folds, and typically last ≤ 14 days in the lips. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- JUVÉDERM® Ultra XC is packaged for single-patient use. Do not resterilize. Do not use if package is opened or damaged.
- In order to minimize the risks of potential complications, this product should only be used by health care professionals 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, patients should be limited to 20 mL of any JUVÉDERM® injectable gel per 60 kg (132 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 facial wrinkles and folds, lips, and perioral area 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® Ultra 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 and it can therefore no longer be assured.
- The safety for use during pregnancy, in breastfeeding females, or in patients under 18 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® Ultra 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 injection sites.
- 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® Ultra 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 Support at 1-877-345-5372.
- If laser treatment, chemical peeling, or any other procedure based on active dermal response is considered after treatment with JUVÉDERM® Ultra XC, there is a possible risk of eliciting an inflammatory reaction at the implant site. An inflammatory reaction is also possible if the product is administered before the skin has healed completely after such a procedure.
- 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® Ultra XC in the Nasolabial Folds (NLFs)

A 2-week, randomized, controlled U.S. clinical study for JUVÉDERM® Ultra XC compared with JUVÉDERM® Ultra without lidocaine showed a similar safety profile in all subjects (N = 36), with the exception of fewer reports of pain/tenderness with the product containing lidocaine. Common treatment site responses by severity and duration, are presented in Tables 1 and 2. Aside from injection site responses, there were no adverse events related to the device, procedure, or anesthesia.

- The most common injection site responses for JUVÉDERM® Ultra XC were redness, swelling, tenderness, firmness, lumps/bumps, discoloration, and bruising.

Table 1. Injection Site Responses by Maximum Severity (Number/% of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM® Ultra XC (N[a] = 36 NLFs)			JUVÉDERM® Ultra (N[a] = 36 NLFs)		
	JUVÉDERM® Ultra XC n[c] %	JUVÉDERM® Ultra n[c] %	Mild n[c] %	Mod[b] n[c] %	Severe n[c] %	Mild n[c] %	Mod[b] n[c] %	Severe n[c] %
Redness	29 81%	30 83%	22 61%	7 19%	0 0%	21 58%	9 25%	0 0%
Pain	17 47%	22 61%	12 33%	5 14%	0 0%	16 44%	5 14%	1 3%
Tenderness	22 61%	29 81%	18 50%	3 8%	1 3%	22 61%	6 17%	1 3%
Firmness	32 89%	33 92%	22 61%	8 22%	2 6%	24 67%	9 25%	0 0%
Swelling	30 83%	29 81%	23 64%	6 17%	1 3%	17 47%	12 33%	0 0%
Lumps/Bumps	20 56%	22 61%	13 36%	6 17%	1 3%	17 47%	4 11%	1 3%
Bruising	27 75%	24 67%	16 44%	8 22%	3 8%	15 42%	6 17%	3 8%
Itching	12 33%	11 31%	12 33%	0 0%	0 0%	10 28%	1 3%	0 0%
Discoloration	22 61%	21 58%	17 47%	2 6%	3 8%	16 44%	3 8%	2 6%

[a] Number of subject NLFs treated with the respective device
[b] Mod = Moderate
[c] Number of NLFs with any occurrence of a particular ISR (or severity for the overall percentages)

Table 2. Duration of Injection Site Responses (Number/% of Subject NLFs)

Injection Site Responses	JUVÉDERM® Ultra XC (N[a] = 36 NLFs) n[b] %				JUVÉDERM® Ultra (N[a] = 36 NLFs) n[b] %			
Duration[c]	1-3 Days	4-7 Days	8-14 Days	> 14 Days	1-3 Days	4-7 Days	8-14 Days	> 14 Days
Redness	22 61%	4 11%	1 3%	2 6%	22 61%	4 11%	2 6%	2 6%
Pain	15 42%	0 0%	1 3%	1 3%	18 50%	3 8%	0 0%	1 3%
Tenderness	14 39%	3 8%	3 8%	2 6%	23 64%	5 14%	0 0%	1 3%
Firmness	15 42%	7 19%	5 14%	5 14%	15 42%	7 19%	8 22%	3 8%
Swelling	19 53%	7 19%	2 6%	2 6%	17 47%	7 19%	3 8%	2 6%
Lumps/Bumps	10 28%	4 11%	2 6%	4 11%	11 31%	5 14%	3 8%	3 8%
Bruising	12 33%	8 22%	4 11%	3 8%	7 19%	8 22%	6 17%	3 8%
Itching	8 22%	3 8%	0 0%	1 3%	9 25%	1 3%	0 0%	1 3%
Discoloration	13 36%	2 6%	4 11%	3 8%	10 28%	5 14%	4 11%	2 6%

[a] Number of subject NLFs treated with the respective device
[b] Number of subject NLFs with each specific ISR by maximum duration
[c] Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation

B. Clinical Evaluation of JUVÉDERM® Ultra (Without Lidocaine) in the NLFs

In the initial randomized, controlled clinical trial to evaluate safety and effectiveness, 146 subjects were injected with JUVÉDERM® Ultra in one NLF and ZYPLAST® dermal filler in the contralateral NLF. Preprinted diary forms were used by subjects to record specific signs and symptoms experienced during each of the first 14 days (day 0 through day 13) after initial and touch-up treatments. Subjects were instructed to rate each common treatment response listed on the diary as "Mild," "Moderate," "Severe," or "None." Injection site responses reported by >5% of subjects in either treatment group are summarized in Tables 3 and 4.

Table 3. Injection Site Responses by Maximum Severity Occurring in > 5% of Treated Subjects (Number/% of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM® Ultra (N[a] = 146 NLFs)			ZYPLAST® (N[a] = 146 NLFs)		
	JUVÉDERM® Ultra n[c] %	ZYPLAST® n[c] %	Mild n[c] %	Mod[b] n[c] %	Severe n[c] %	Mild n[c] %	Mod[b] n[c] %	Severe n[c] %
Redness	136 93%	130 89%	72 49%	48 33%	16 11%	69 47%	45 31%	16 11%
Pain/ Tenderness	131 90%	128 88%	74 51%	45 31%	12 8%	87 60%	34 23%	7 5%
Firmness	129 88%	127 87%	66 45%	53 36%	10 7%	60 41%	56 38%	11 8%
Swelling	125 86%	122 84%	60 41%	54 37%	11 8%	77 53%	37 25%	8 5%
Lumps/Bumps	115 79%	122 84%	61 42%	45 31%	9 6%	66 45%	42 29%	14 10%
Bruising	86 59%	80 55%	43 29%	29 20%	14 10%	47 32%	27 18%	6 4%
Itching	52 36%	53 36%	42 29%	5 3%	5 3%	43 29%	7 5%	3 2%
Discoloration	48 33%	49 34%	31 21%	11 8%	6 4%	31 21%	15 10%	3 2%

[a] Number of subject NLFs treated with the respective device
[b] Mod = Moderate
[c] Number of subject NLFs with each specific ISR

Table 4. Duration of Injection Site Responses Occurring in > 5% of Treated Subjects (Number/% of Subject NLFs)

Injection Site Responses	JUVÉDERM® Ultra (N[a] = 146 NLFs) n[b] %				ZYPLAST® (N[a] = 146 NLFs) n[b] %			
Duration[c]	≤ 3 Days	4-7 Days	8-14 Days	> 14 Days	≤ 3 Days	4-7 Days	8-14 Days	> 14 Days
Redness	60 41%	50 34%	8 5%	18 12%	46 32%	46 32%	10 7%	28 19%
Pain/ Tenderness	61 42%	46 32%	18 12%	6 4%	49 34%	53 36%	14 10%	12 8%
Firmness	29 20%	34 23%	20 14%	46 32%	25 17%	28 19%	20 14%	54 37%
Swelling	38 26%	48 33%	22 15%	17 12%	54 37%	38 26%	20 14%	10 7%
Lumps/Bumps	26 18%	32 22%	18 12%	39 27%	16 11%	18 12%	19 13%	69 47%
Bruising	29 20%	28 19%	24 16%	5 3%	35 24%	27 18%	10 7%	8 5%
Itching	25 17%	15 10%	7 5%	5 3%	21 14%	17 12%	4 3%	11 8%
Discoloration	22 15%	12 8%	4 3%	10 7%	26 18%	9 6%	3 2%	11 8%

[a] Number of subject NLFs treated with the respective device
[b] Number of subject NLFs with each specific ISR by maximum duration
[c] Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation

Local injection site responses were recorded in subjects' diaries one or more times for 99% of JUVÉDERM® Ultra treated NLFs and 98% of ZYPLAST® treated NLFs. Subjects' scores for both products were predominantly Mild or Moderate in intensity, and their duration was short lasting (7 days or less). JUVÉDERM® Ultra injection site responses reported by greater than 1% of subjects and not noted in the above tables were skin dryness and peeling. No clinically meaningful differences in the safety profiles of JUVÉDERM® Ultra and ZYPLAST® were found during the study.

C. Clinical Evaluation of JUVÉDERM® Ultra XC for Lip Augmentation

In a randomized, controlled clinical trial to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC for lip augmentation, 213 subjects were randomized to treatment and received injections in the lips and perioral area (N = 157), or to delayed-treatment control, and had treatment delayed 3 months (N = 56).

Preprinted diary forms were used by subjects to record specific signs and symptoms of ISRs experienced during the 30 days (Day 1 through Day 30) following initial treatment, touch-up treatment (if performed), and repeat treatment. Subjects were instructed to rate each ISR listed on the diary as Mild, Moderate, Severe, or None.

- Mild ISRs were defined as having little, if any discomfort and having no effect on daily activities.
- Moderate ISRs were defined as causing some discomfort and having some effect on daily activities.
- Severe ISRs were defined as causing great discomfort and events that would compromise performance of daily activities.

ISRs reported by > 5% of the 193 subjects who completed post-treatment diary forms after initial treatment are summarized in Table 5. The majority of ISRs were Mild or Moderate in intensity, and their duration was short lasting (14 days or less). ISRs reported after touch-up treatment and repeat treatment were similar to those reported after initial treatment.

Table 5. Injection Site Responses after Initial Treatment Occurring in > 5% of Treated Subjects after Lip Augmentation by Severity and Duration

Injection Site Responses	Severity[a]			Duration[b]				Subjects N = 193[c]
	Mild	Moderate	Severe	< 3 Days	4-7 Days	8-14 Days	15-30 Days	
	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %[d]	n %
Swelling	45 24%	94 51%	46 25%	51 28%	63 34%	51 28%	20 11%	185 96%
Bruising	35 19%	84 47%	61 34%	31 17%	91 51%	46 26%	12 7%	180 93%
Firmness	53 31%	91 53%	29 17%	38 22%	43 25%	55 32%	37 21%	173 90%
Lumps/Bumps	59 35%	81 48%	29 17%	41 24%	32 19%	44 26%	52 31%	169 88%
Tenderness	75 46%	64 39%	26 16%	56 34%	41 25%	53 32%	15 9%	165 86%
Redness	55 36%	69 46%	27 18%	69 46%	49 33%	27 18%	6 4%	151 78%
Pain	70 49%	60 42%	13 9%	93 65%	28 20%	19 13%	3 2%	143 74%
Discoloration	36 51%	25 36%	9 13%	37 53%	8 11%	21 30%	4 6%	70 36%
Itching	34 61%	18 32%	4 7%	37 66%	11 20%	6 11%	2 4%	56 29%
Peeling	5 39%	7 54%	1 8%	9 69%	1 8%	3 23%	0 0%	13 7%

[a] Maximum reported severity
[b] Maximum reported successive occurrence of treatment response
[c] Number of subjects who completed the diary
[d] Percentage based on number of subjects reporting each specific ISR

ISRs that lasted beyond the 30-day diaries were considered adverse events. Adverse events were also reported by the Treating Investigator at follow-up visits. After initial treatment (or touch-up treatment if performed), a total of 168 treatment-related adverse events were reported in 29% of subjects (60/208). In general, AEs were mild (77%, 130/168) or moderate (16%, 27/168), resolved without sequelae (93%, 156/168), and required no action (91%, 153/168). AEs typically resolved within 3 months. Treatment-related adverse events that occurred in > 1% of subjects were injection site mass 16% (33/208), induration 10% (21/208), discoloration 5% (10/208), pain 4% (9/208), bruising 3% (7/208), swelling 3% (7/208), erythema 2% (4/208), and reaction 2% (4/208). Similar AEs were reported after repeat treatment.

In the clinical study, 11 severe treatment-related adverse events occurred in 4 subjects. These adverse events include angioedema and injection site mass, pain, bruising, swelling, erythema, and hypertrophy. All of these events resolved without sequelae, and all except the angioedema required no action. One subject experienced angioedema in the upper lip following topical anesthetic application of 25% lidocaine/7% tetracaine and injection of JUVÉDERM® Ultra XC, which resolved following administration of oral anti-histamine, hyaluronidase injection, and oral anti-inflammatory medication.

Functional features of the lips, including lip sensitivity, sensation, and speech were assessed before treatment and at follow-up visits after treatment. Minimal changes were noted in subject self-assessments of the function and sensation of the lips and mouth area, Treating Investigator assessments of other functional features of the lips and mouth area, Evaluating Investigator assessments of subjects' lip sensitivity, and speech and language pathologist assessments of subjects' speech and articulation at scheduled time points following treatment, thus demonstrating that lip function and sensation were unaffected by treatment with JUVÉDERM® Ultra XC.

Subgroup analyses were completed to analyze ISRs and AEs in relation to Fitzpatrick Skin Phototype, age, investigational site, gender, volume injected, plane of injection, injection technique, and injection site. No increased safety risks were observed for any specific groups.

D. Other Safety Data

Other Clinical Studies

In 2 additional randomized US clinical studies of other JUVÉDERM® formulations (without lidocaine) in a total of 293 subjects, the safety profile was similar to that described above for JUVÉDERM® Ultra.

Postmarket Surveillance

The following adverse events were received from postmarket surveillance for JUVÉDERM® Ultra and Ultra Plus, 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 adverse events obtained through postmarket surveillance are listed in order of number of reports received: edema, lack or loss of correction, inflammatory reaction, non-inflammatory nodule, hematoma, pain, unsatisfactory result, allergic reaction, vascular occlusion, skin discoloration, device migration, neurological symptoms such as increase or decrease in sensation, infection, blister, inflammatory nodule/granuloma, dermatitis, anxiety, dry skin, overcorrection, necrosis, bleeding, herpes, headache, flu-like symptoms, varied injuries, angioedema, scarring, abscess, vision abnormalities, acne, drainage, malaise, dizziness, dyspnea, cyst, extrusion, nausea, cardiac complications, syncope, depression, telangiectasia, traumatic injury, calcification, autoimmune disorder exacerbation, beading, deeper wrinkle, and vision loss.

In many cases, the symptoms resolved without any treatment. Reported treatments have included: antibiotics, steroids, steroidal creams, hyaluronidase, anti-inflammatories, anti-histamines, needle aspiration and drainage, ultrasound therapy, analgesics, anti-viral, excision, eye drops, hyperbaric oxygen, laser resurfacing, tissue debridement, surgical scar revision, ice, massage, warm compress, anticholinergics, vasodilators, arnica, petroleum jelly, anxiolytics, antifungals, anticoagulants, and epinephrine.

Vascular occlusion of vessels resulting in necrosis and vision abnormalities have been reported following injection of JUVÉDERM® products, with and without lidocaine, with a time to onset ranging from immediate to within one week following injection. These reported events likely resulted from inadvertent arterial injection. In many of these cases, the product was injected into the highly vascularized areas of the glabella, nose, and periorbital area, which are outside the device indications for use (see WARNINGS section). Reported treatments include: anticoagulants, epinephrine, aspirin, hyaluronidase, steroid treatment, eye drops, hyperbaric oxygen, surgery, vasodilators, and warm compress. Outcomes have ranged from completely resolved to ongoing at the time of last contact.

Delayed-onset inflammation near the site of dermal filler injections is one of the known adverse events associated with dermal fillers. Cases of delayed-onset inflammation have been reported to occur at the dermal filler treatment site following viral or bacterial illnesses or infections, vaccinations, or dental procedures. Typically, the reported inflammation was responsive to treatment or resolved on its own.

Adverse reactions should be reported to Allergan® Product Surveillance Department at 1-877-345-5372.

7. CLINICAL STUDIES

A. Pivotal Study for JUVÉDERM® Ultra (Without Lidocaine) for Treatment of NLFs

Pivotal Study Design

A prospective, double-blind, randomized, within-subject, controlled, multicenter, pivotal, clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra in the treatment of moderate to severe wrinkles. Subjects underwent treatment with JUVÉDERM® Ultra in one NLF and the control implant (ZYPLAST® bovine collagen) in the opposite NLF.

Up to 3 bilateral treatments (initial treatment and up to 2 touch-up treatments), approximately 2 weeks apart, were allowed. At 2 and 4 weeks after each treatment, the Independent Expert Reviewer (IER) assessed the level of correction achieved. If correction was less than optimal after the first or second treatment, the Investigator re-treated the under-corrected NLFs using the same respective treatment materials as in the initial treatment. The IER and the subject remained masked to the randomized treatment assignment.

Routine follow-up visits for safety and effectiveness occurred at days 3 and 7 and week 2 after each treatment, and at 4, 8, 12, 16, 20, and 24 weeks after the last treatment. Standardized facial photography was performed for documentation purposes. The Investigator and the IER independently evaluated the severity of the subject's NLFs using the validated 5-point (range 0 to 4) photographic Allergan® NLF severity scale. The subject made independent self-assessments of NLF severity using a non-photographic 5-point grading scale.

Study Endpoints

The primary effectiveness endpoint for the study was the IER's NLF severity score over the post-treatment follow-up period. Effectiveness of device treatment was demonstrated by a lowering of the NLF severity score. Additional analyses included the subject's and the Investigator's live NLF severity assessments.

Subject Demographics

A total of 146 subjects (31 to 75 years of age) were randomized and treated, and 140 (96%) completed the 6-month follow-up period. Prior to enrollment, 87 (60%) had previous experience with other facial dermal treatments (eg, alpha-hydroxy agents, neurotoxin, microdermabrasion, or retinoic acid).

Subject demographics and pretreatment characteristics of the JUVÉDERM® Ultra effectiveness population are presented in Table 6.

Table 6. Demographics and Pretreatment Characteristics of the Effectiveness Population (Number/% of Subjects) N = 146

Gender (Number/%)		
Female	135	92%
Male	11	8%
Ethnicity (Number/%)		
Caucasian	105	72%
African American	18	12%
Hispanic	15	10%
Asian	7	5%
Other	1	1%
Fitzpatrick Skin Phototype (Number/%)		
I	4	3%
II	34	23%
III	55	38%
IV	24	16%
V	24	16%
VI	5	3%
Mean Baseline NLF Severity Score[a]		
JUVÉDERM® Ultra NLF	2.6	
ZYPLAST® NLF	2.6	

[a] NLF severity was ranked on a 5-point scale from None (0) to Extreme (4)

Effectiveness Results

The primary effectiveness results for JUVÉDERM® Ultra based on the IER's assessment of NLF severity are presented in Table 7.

Table 7. Effectiveness Summary Independent Expert Reviewer's NLF Severity Scores

		JUVÉDERM® Ultra (N[a] = 146 NLFs)		Control[b] (N[a] = 146 NLFs)	
	n[c]	NLF Severity[d]	Improvement Since Baseline[d]	NLF Severity[d]	Improvement Since Baseline[d]
Baseline	146	2.6	–	2.6	–
Week 2	142	0.6	2.0	0.7	1.9
Week 12	129	0.9	1.7	1.6	0.9
Week 24	138	1.3	1.3	2.3	0.3

[a] Number of subject NLFs treated with the respective device
[b] A commercially available injectable bovine collagen implant
[c] Number of subject NLFs with data at baseline and the specified time point
[d] Mean score

Throughout the 24-week study period, JUVÉDERM® Ultra provided a clinically and statistically significant improvement in NLF severity. Clinical superiority was achieved at week 24 for JUVÉDERM® Ultra over ZYPLAST® with mean NLF severity of 1.3 and 2.3, respectively (P <0.0001). Additionally, subject assessments for product preference overwhelmingly favored JUVÉDERM® Ultra: 88% preferred the JUVÉDERM® Ultra treated NLF over the ZYPLAST® treated NLF.

B. Extended Follow-up Clinical Study

Of the 146 randomized and treated subjects, more than three-quarters (79%, 116/146) returned after completion of their 24-week follow-up in the pivotal study for complimentary repeat treatment. Demographics for the subjects receiving repeat treatment were similar to those in the overall study. The majority of subjects were Caucasian and female, with a median age of 50 years. More than one-third of subjects were of Fitzpatrick Skin Phototypes IV, V, or VI.

After completing the 24-week study, subjects returned for repeat treatment at their convenience or their Investigator's convenience. The average time elapsed between last initial treatment and repeat treatment was approximately 9 months. A statistical analysis demonstrated that those subjects who returned for repeat treatment at a later time point were representative of the pivotal study subjects overall. There were no significant differences between these stratified groups in terms of NLF severity at baseline or at the 24-week follow-up visit or overall initial volume injected. Before repeat treatment, live assessments of wrinkle severity were made by the Investigator and the subject. The extended follow-up effectiveness results for JUVÉDERM® Ultra based on the Investigator's assessment of NLF severity are presented in Table 8.

Table 8. Extended Follow-up Prior to Repeat Treatment Effectiveness Summary Investigator's NLF Severity Scores

		JUVÉDERM® Ultra (N[a] = 116 NLFs)		
	n[b]	NLF Severity[c]	Improvement Since Baseline[c]	*P* value
Baseline[a]	116	2.6	–	N/A
Follow-up Week 24[a] **(Month 6)**	116	1.3	1.3	< .0001
Follow-up Weeks 25-36 (Months 6-9)	68	1.3	1.2	< .0001
Follow-up Weeks > 36 (> 9 months)	48	1.6	1.1	< .0001

[a] Data collected during pivotal study
[b] Number of subject NLFs with data at baseline and the specified time point
[c] Mean score

All subjects returning for repeat treatment were stratified into 2 groups based on the time elapsed between last initial treatment and repeat treatment: 25 to 36 weeks or > 36 weeks. Mean improvement since baseline was clinically significant (≥ 1 point) for both groups, with a large majority of subjects treated with JUVÉDERM® Ultra demonstrating improvement:

- 84% (57/68) at 25 to 36 weeks (6-9 months)
- 75% (36/48) beyond 36 weeks (beyond 9 months)

Follow-up After Repeat Treatment

A subset of subjects enrolled in a prospective, multicenter study for follow-up after repeat treatment. Subjects were eligible for the follow-up study if they completed the pivotal study, indicated that they preferred JUVÉDERM® Ultra over the control device, and received repeat treatment between 24 and 36 weeks after their last treatment in the pivotal study.

Subjects underwent repeat treatment with JUVÉDERM® Ultra in both NLFs. Demographics for subjects enrolled in the repeat treatment extended follow-up study were similar to those in the pivotal study. Routine follow-up visits for safety and effectiveness occurred at 4, 12, 24, 36, and 48 weeks after the repeat treatment. The Investigator evaluated each subject for signs and symptoms of serious or unanticipated adverse events. The Investigator also evaluated the severity of the subject's NLFs using the validated 5-point (range 0 to 4) photographic Allergan® NLF severity scale. The subject made independent self-assessments of NLF severity using the nonphotographic 5-point grading scale.

No serious or unanticipated adverse events were reported. The effectiveness results for repeat treatment with JUVÉDERM® Ultra based on the Investigator's assessment of NLF severity after repeat treatment are presented in Table 9.

Table 9. Follow-up after Repeat Treatment Effectiveness Summary Investigator's NLF Severity Scores

		JUVÉDERM® Ultra N = 24	
	n[a]	NLF Severity[b]	Improvement Since Baseline[b]
Baseline	24	2.5	–
Pre-repeat Treatment	24	1.4	1.1
Week 12	23	0.9	1.7
Week 24	23	1.1	1.4
Week 48	9	1.3	1.3

[a] Number of subject NLFs with data at baseline and the specified time point
[b] Mean score

Throughout the 48-week follow-up period, JUVÉDERM® Ultra provided a clinically significant improvement in NLF severity (≥ 1 point mean improvement) with a large majority of subjects treated with JUVÉDERM® Ultra demonstrating improvement at 24 weeks and beyond: 87% (20/23) at 24 weeks and 78% (7/9) at 48 weeks (1 year).

C. Clinical Study for JUVÉDERM® Ultra XC for Treatment of NLFs

A prospective, double-blind, randomized, within-subject, controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC compared with JUVÉDERM® Ultra without lidocaine. The purpose of this study was to evaluate the level of procedural pain (pain during injection) experienced by subjects when treated with each product. The duration of the study was 2 weeks.

A total of 36 subjects received a single treatment with JUVÉDERM® Ultra XC in one NLF and JUVÉDERM® Ultra without lidocaine in the other NLF. Within 30 minutes after both NLFs were treated, the subjects rated procedural pain on an 11-point scale and a 5-point comparative scale. Both the Investigators and subjects rated NLF severity at baseline and 2 weeks after treatment using the 5-point NLF severity scale from the pivotal study. Subjects utilized an interactive voice-response-system diary to record common treatment site reactions for 14 days.

Most of the subjects were women (94%) of Caucasian descent (75%) with Fitzpatrick Skin Phototype II or III (58%). Persons of color (Fitzpatrick Skin Phototypes IV, V, or VI) comprised 36% of treated subjects. Median age at study entry was 52 years (range, 32 to 73). Subject demographics are shown in Table 10.

Table 10. Subject Demographics (Number/% of Subjects) N = 36 Subjects

Gender		
Female	34	94%
Male	2	6%
Ethnicity		
Caucasian	27	75%
African American	7	19%
Hispanic	0	0%
Asian	1	3%
Other	1	3%
Fitzpatrick Skin Type		
I	2	6%
II	16	44%
III	5	14%
IV	7	19%
V	3	8%
VI	3	8%

The pain scores for the NLFs treated with JUVÉDERM® Ultra XC were significantly lower (P < 0.0001) than for the NLFs treated with JUVÉDERM® Ultra without lidocaine (Table 11) based on the 11-point scale. On the comparative scale, 94% (34/36) of subjects rated the side with lidocaine as less or slightly less painful compared to the side without lidocaine (Table 12).

Table 11. Subject Assessment of Procedural Pain Scores (N = 36)

	Mean Pain Score[a]
JUVÉDERM® Ultra XC	1.5
JUVÉDERM® Ultra	5.2
Mean Difference	-3.7

[a] Procedural pain score ranges from 0 to 10 where 0 = No Pain and 10 = Worst Pain Imaginable

Table 12. Subject Assessments of Comparative Procedural Pain Score

	JUVÉDERM® Ultra (N = 36 NLFs) N (%)
JUVÉDERM® Ultra XC is less painful	23 (64%)
JUVÉDERM® Ultra XC is slightly less painful	11 (31%)
No difference between products	0 (0%)
JUVÉDERM® Ultra XC is slightly more painful	2 (6%)
JUVÉDERM® Ultra XC is more painful	0 (0%)

NLF severity improvement after 2 weeks was similar for both JUVÉDERM® products (with and without lidocaine). The mean baseline score was 2.3, and a clinically significant improvement (severity reduction) to 0.7 was observed after 2 weeks for both products.

D. Pivotal Study of JUVÉDERM® Ultra XC for Lip Augmentation

A prospective, single-blind, randomized, no-treatment controlled, multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra XC for injection into the lips and perioral area (vermilion, vermilion border, philtral columns, Cupid's bow, perioral lines, and/or oral commissures) for lip augmentation. A total of 213 subjects were randomized to either treatment with JUVÉDERM® Ultra XC (N = 157) or to delayed-treatment control (N = 56), and had treatment delayed approximately 3 months.

Treatment group subjects underwent treatment with JUVÉDERM® Ultra XC at the outset of the study, followed by an optional touch-up treatment 2-4 weeks after the initial treatment, if deemed necessary to achieve optimal correction. The primary follow-up period consisted of office visits at 1 and 3 months after the last treatment. Control subjects also completed 1 and 3 month follow-up visits. Thereafter, control subjects crossed over to initiate the study treatment and touch-up with post-treatment follow-up identical to the treatment group.

All subjects continued through an extended follow-up period, which consisted of safety and effectiveness follow-up visits at 6, 7½, 9, 10½, and 12 months after their last treatment, or until the visit at which the Independent Evaluating Investigator's assessment of the subject's overall Lip Fullness score returned to or was lower than the baseline score, whichever occurred first. Subjects were then eligible for a repeat treatment, with post-treatment follow-up for up to 6 months after repeat treatment, at which time all subjects completed the study.

Study Endpoints

The primary effectiveness endpoint for the study was the blinded Evaluating Investigator's assessment of the subject's overall Lip Fullness on the validated 5-point Allergan® Lip Fullness Scale (LFS). A responder was defined as a subject with ≥1 point improvement in overall lip fullness score compared with the pre-treatment score on the LFS. Effectiveness was demonstrated if at least 60% of subjects treated with JUVÉDERM® Ultra XC were observed to be responders and if the responder rate for treated subjects was statistically superior to the responder rate for the no-treatment control group at 3 months after treatment.

Secondary measures included the Evaluating Investigators' assessments of the subject's upper and lower lip fullness, the severity of the subject's perioral lines and oral commissures, as well as the subjects' assessments of whether their lip fullness goal was achieved.

Additional effectiveness measures included Evaluating Investigator assessment of the treatment area using the Other Aesthetic Features of the Lips and Mouth Area questionnaire, changes in the surface area and volume of the lips as calculated from 3D imaging, subject self-assessments of the look and feel of the lips and mouth, as well as subject assessments of willingness to undergo treatment again.

Subject Demographics

Subject demographics and pretreatment characteristics of the treatment and control group are presented in Table 13.

Table 13. Subject Demographics and Pretreatment Characteristics (N = 213)

	Treatment Group (N = 157) % (n/N)	Control Group (N = 56) % (n/N)
Gender		
Female	95.5% (150/157)	96.4% (54/56)
Male	4.5% (7/157)	3.6% (2/56)
Ethnicity		
Caucasian	84.7% (133/157)	85.7% (48/56)
Hispanic	5.1% (8/157)	3.6% (2/56)
African American	8.3% (13/157)	5.4% (3/56)
Asian	0.6% (1/157)	3.6% (2/56)
Other	1.3% (2/157)	1.8% (1/56)
Fitzpatrick Skin Phototype		
I	1.3% (2/157)	5.4% (3/56)
II	36.9% (58/157)	32.1% (18/56)
III	45.9% (72/157)	44.6% (25/56)
IV	3.8% (6/157)	7.1% (4/56)
V	10.2% (16/157)	8.9% (5/56)
VI	1.9% (3/157)	1.8% (1/56)
Baseline Overall Lip Fullness (LFS[a]) Score		
Minimal	30.6% (48/157)	33.9% (19/56)
Mild	59.9% (94/157)	53.6% (30/56)

[a] Lip Fullness was rated on the 5-point LFS from Minimal (1) to Very Marked (5)

Effectiveness Results

JUVÉDERM® Ultra XC provided a clinically and statistically significant improvement in overall lip fullness compared to the no-treatment control group at Month 3. The primary effectiveness criteria were met in that the treatment group's responder rate of 79.1% was greater than the 60% threshold, and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (26.1%).

Throughout the extended follow-up period, JUVÉDERM® Ultra XC continued to provide a clinically significant improvement in lip fullness (≥ 1 point mean improvement on the LFS), with a majority of subjects treated with JUVÉDERM® Ultra XC demonstrating improvement through 12 months (Table 14).

Table 14. Effectiveness of JUVÉDERM® Ultra XC in the Lips Through 1 Year

	n[a]	Treatment Group (N = 157) Responder Rate % (n)
Baseline[a]	157	N/A
1 Month	139	79.9% (111)
3 Months	139	79.1% (110)
6 Months	118	80.5% (95)
9 Months	99	63.6% (63)
12 Months	101	56.4% (57)

[a] Number of subjects with data at baseline and the specified time point

At Month 3, improvements in upper and lower lip fullness were observed in 75.4% (104/138) and 79.9% (107/134), respectively, based on Evaluating Investigator assessments. While the responder rates for improvement in perioral lines and oral commissures at Month 3 were 47.5% (29/61) and 47.3% (114/241), respectively, demonstrating some improvement in severity of upper lip perioral lines and oral commissures, inadequate information was available regarding the clinical and statistical significance of this improvement. Thus, the treatment benefit for perioral lines and oral commissures was not determined in this lip augmentation study.

At 3 months, 81.8% (112/137) of subjects rated that their overall lip fullness goals were achieved, and 87.5% (119/136) of subjects assessed their treatment outcome as expected or better than expected. The majority of subjects (89.1%, 123/138) indicated willingness to undergo treatment again at Month 3, which remained high at the end of the extended follow-up period, with 84.7% (72/85) indicating willingness to undergo treatment again. Using the Other Aesthetic Features questionnaire, Evaluating Investigators assessed their satisfaction with the subject's lips and mouth area, with over 75% of subjects assessed as improved through Month 12.

At 3 months, 92.1% (128/139) of subjects rated an improvement in overall satisfaction with the look and feel of their lips and mouth, which lasted through Month 12 for 78.4% (58/74) of subjects. The majority of subjects also reported improvement in the softness, smoothness, and natural look and feel of their lips and mouth through 12 months.

Objective lip measurements calculated from the 3D imaging showed an increase in both lip volume and overall lip surface area. At Month 3, treatment group subjects showed a mean increase in lip volume of 0.61 cc and a 25% increase in surface area (N = 130), while control group subjects showed almost no increase in lip volume and an 8% increase in surface area (N = 44). Treatment group subjects showed an increase in these measurements at later time points that gradually tapered off to a mean lip volume increase of 0.54 cc and a 19% surface area increase at Month 12 (N = 54).

No differences in overall lip fullness responder rates at Month 3 were observed based on the following subgroup analyses: baseline lip fullness, gender, race, investigational site, plane of injection, injection technique, injection volume, injection site, and Fitzpatrick Skin Phototype.

Follow-Up After Repeat Treatment

Repeat treatment was administered to 114 subjects. The effectiveness profile after repeat treatment was similar to that after the initial treatment. At Month 3 after repeat treatment, the responder rate was similar to that after initial treatment, with 85.5% of subjects showing at least a 1-point improvement in lip fullness, based on the Evaluating Investigator assessment (Table 15).

Table 15. Effectiveness of JUVÉDERM® Ultra XC after Repeat Treatment

	n[a]	Responder Rate % (n)
Month 1	71	87.3% (62)
Month 3	76	85.5% (65)

[a] Number of subjects with data at baseline and the specified time point

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® 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

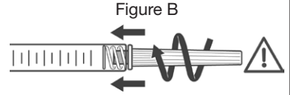


Figure C

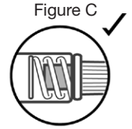
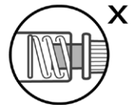


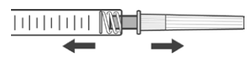
Figure D



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® Ultra XC injectable gel is a highly cross-linked smooth gel formulation that can be injected using a fine gauge (e.g., 30-G) needle for more versatility in contouring and volumizing of facial wrinkles and folds and lips.
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. Depending on the type of skin, best results are obtained when the defect is readily distensible and correction can be visualized by manual manipulation (stretching) of the skin. Pretreatment photographs are recommended.
4. Although study results showed JUVÉDERM® Ultra XC to be less painful than JUVÉDERM® Ultra, supplementary anesthesia may be used for additional pain management during and after injection.
5. After ensuring that the patient has thoroughly washed the treatment area with soap and water, the area should be swabbed with alcohol or other antiseptic. Prior to injecting, depress the plunger rod until the product flows out of the needle.
6. 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.
7. The injection technique for wrinkles, folds, and lips may vary with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered. A linear threading technique, serial puncture injections, fanning technique, cross-hatching technique, or a combination have been used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or discoloration.
8. Inject JUVÉDERM® Ultra XC by applying even pressure on the plunger rod while slowly pulling the needle backwards. It is important that the injection be stopped just before the needle is pulled out of the skin to prevent material from leaking out or ending up too superficially in the skin.
9. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
10. The typical total volume to achieve optimal correction of moderate to severe nasolabial folds is 1.6 mL per treatment site. The typical volume to achieve optimal correction for repeat treatment is 0.7 mL per treatment site.
11. The typical volume injected into the lips and perioral area to achieve optimal correction for lip augmentation is approximately 2.2 mL, which may vary depending on the goals the patient wishes to achieve. Injection volumes into the lips and perioral area after repeat treatment tended to be lower, with the typical total injection volume to achieve optimal correction being approximately 1.5 mL.
12. 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.
13. 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]
14. When injection is completed, the treated site should be gently massaged so that it 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.
15. 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 to a touch-up session after 1-2 weeks.
16. Patients may have mild to moderate injection site responses, which typically resolve in a few days in the NLFs, and within 2 weeks in the lips and perioral area. If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period.

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

17. After the initial treatment, an additional treatment (from 1 to 4 weeks later) may be necessary to achieve the desired level of correction. If further treatment is needed, 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 treatment goals, wrinkle severity, lip fullness, skin elasticity, and dermal thickness at the treatment site.
18. The health care professional should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of JUVÉDERM® Ultra 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, extensive sun or heat exposure, and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.
- To report an adverse reaction, phone the Allergan® Product Support Department, 1-877-345-5372.

9. HOW SUPPLIED

JUVÉDERM® Ultra XC injectable gel is supplied in individual treatment syringes with 30-G needles for single-patient use and ready for injection (implantation). 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 opened or damaged.

10. SHELF LIFE AND STORAGE

JUVÉDERM® Ultra 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® Ultra 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 Support immediately at 1-877-345-5372.

To place an order, contact Allergan® at 1-800-377-7790.

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