



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 injectable gel is a sterile, biodegradable, nonpyrogenic, viscoelastic, clear, colorless, homogenized gel implant. JUVÉDERM® Ultra injectable gel consists of crosslinked hyaluronic acid (HA) produced by *Streptococcus equi* bacteria, formulated to a concentration of 24 mg/mL and suspended in a physiologic buffer.

2. INTENDED USE/INDICATIONS

JUVÉDERM® Ultra 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).

3. CONTRAINDICATIONS

- JUVÉDERM® Ultra injectable gel is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
- JUVÉDERM® Ultra injectable gel contains trace amounts of gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

4. WARNINGS

- JUVÉDERM® Ultra injectable gel must not be injected into blood vessels. Introduction of JUVÉDERM® Ultra injectable gel into the vasculature may occlude the vessels and could cause infarction or embolization.
- Use of JUVÉDERM® Ultra injectable gel 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 procedure reaction to JUVÉDERM® Ultra injectable gel has been observed as consisting mainly of short-term inflammatory symptoms starting early after treatment and with less than 7 days' duration. Refer to the ADVERSE EVENTS section for details.

5. PRECAUTIONS

- JUVÉDERM® Ultra injectable gel is packaged for single-patient use. Do not resterilize. Do not use if package is opened or damaged.
- Based on preclinical studies, patients should be limited to 20 mL of JUVÉDERM® Ultra 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 of JUVÉDERM® Ultra injectable gel for the treatment of anatomic regions other than facial wrinkles and folds (eg, lips) have not been established in controlled clinical studies.
- As with all transcutaneous procedures, JUVÉDERM® Ultra injectable gel implantation carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- JUVÉDERM® Ultra 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 of JUVÉDERM® Ultra injectable gel for use during pregnancy, in breastfeeding females, or in patients under 18 years has not been established.
- The safety of JUVÉDERM® Ultra injectable gel in patients with known susceptibility to keloid formation, hypertrophic scarring, and pigmentation disorders has not been studied.
- JUVÉDERM® Ultra injectable gel 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 injectable gel is a clear, colorless gel without 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 injectable gel, there is a possible risk of eliciting an inflammatory reaction at the implant site. This also applies if JUVÉDERM® Ultra injectable gel 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-lock and needle hub connection.

6. ADVERSE EVENTS

A. Clinical Evaluation of JUVÉDERM® Ultra injectable gel

In a randomized, controlled clinical trial to evaluate safety and effectiveness, 146 subjects were injected with JUVÉDERM® Ultra injectable gel in one nasolabial fold (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 1 and 2.

Table 1. 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 injection-site response

Table 2. 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 %			
	≤ 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 injection-site response 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 injectable gel treated NLFs and 98% of ZYPLAST® dermal filler 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 injectable gel 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 injectable gel and ZYPLAST® dermal filler were found during the study.

B. Other Safety Data

In 2 additional randomized US clinical studies of other JUVÉDERM® injectable gel formulations with a total of 293 subjects, the safety profile was similar to that described above for JUVÉDERM® Ultra injectable gel.

Postmarket safety surveillance of JUVÉDERM® injectable gel in countries outside the US indicates that the most common adverse events include swelling, redness, discoloration, and bruising.

7. CLINICAL STUDY

A. 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 injectable gel in the treatment of moderate to severe wrinkles. Subjects underwent treatment with JUVÉDERM® Ultra injectable gel in one NLF and the control implant (ZYPLAST® dermal filler 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 undercorrected 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 a validated 5-point (range 0 to 4) photographic NLF severity scale. The subject made independent self-assessments of NLF severity using a nonphotographic 5-point grading scale.

B. 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.

C. 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, BOTOX® Cosmetic [onabotulinumtoxinA], microdermabrasion, or retinoic acid).

Subject demographics and pretreatment characteristics of the JUVÉDERM® Ultra injectable gel effectiveness population are presented in Table 3.

**Table 3. 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)

D. Effectiveness Results

The primary effectiveness results for JUVÉDERM® Ultra injectable gel based on the IER's assessment of NLF severity are presented in Table 4.

Table 4. Effectiveness Summary Independent Expert Reviewer's NLF Severity Scores

	n ^c	JUVÉDERM® Ultra (N ^a = 146 NLFs)		Control ^b (N ^a = 146 NLFs)	
		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 injectable gel provided a clinically and statistically significant improvement in NLF severity. Clinical superiority was achieved at Week 24 for JUVÉDERM® Ultra injectable gel over ZYPLAST® dermal filler with mean NLF severity of 1.3 and 2.3, respectively ($P < .0001$). Additionally, subject assessments for product preference overwhelmingly favored JUVÉDERM® Ultra injectable gel: 88% preferred the JUVÉDERM® Ultra injectable gel treated NLF over the ZYPLAST® dermal filler treated NLF.

8. ADDITIONAL CLINICAL INFORMATION

Of the 146 randomized and treated subjects, more than three-quarters (79%, 116/146) returned after completion of their 24-week followup 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.

Subjects returned for repeat treatment at their (or their Investigator's) convenience after completion of the 24-week study. 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 timepoint 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 injectable gel based on the Investigator's assessment of NLF severity are presented in Table 5.

Table 5. Extended Follow-up Prior to Repeat Treatment Effectiveness Summary Investigator's NLF Severity Scores

	JUVÉDERM® Ultra (N = 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 injectable gel demonstrating improvement:

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

B. 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 injectable gel 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 injectable gel 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 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 injectable gel based on the Investigator's assessment of NLF severity after repeat treatment are presented in Table 6.

Table 6. 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

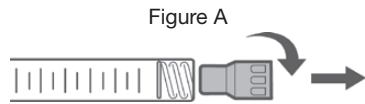
Throughout the 48-week follow-up period, JUVÉDERM® Ultra injectable gel provided a clinically significant improvement in NLF severity (≥ 1 -point mean improvement) with a large majority of subjects treated with JUVÉDERM® Ultra injectable gel demonstrating improvement at 24 weeks and beyond: 87% (20/23)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

9. 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.



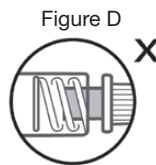
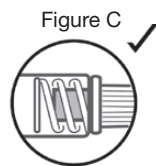
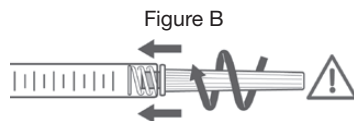
STEP 2: Insert needle

Hold the syringe body and firmly insert the hub of the needle (provided in the JUVÉDERM® package) into the luer-lock end of the syringe.

STEP 3: Tighten the needle

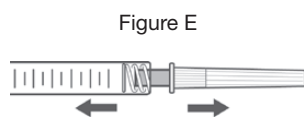
Tighten the needle by turning it firmly in a clockwise direction (see Figure B) until it is seated in the proper position, as shown in Figure C.

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.



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.



B. Physician Instructions

1. JUVÉDERM® Ultra injectable gel is a highly crosslinked formulation that can be injected using a 30-G needle for more versatility in contouring and volumizing of facial wrinkles and folds. Prior to treatment with JUVÉDERM® Ultra injectable gel, 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.
2. 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.
3. Topical or injectable anesthesia may be used to manage pain during and after injection.
4. 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 JUVÉDERM® Ultra injectable gel, depress the plunger rod until the product flows out of the needle.
5. The injection technique of JUVÉDERM® Ultra injectable gel with regard to the angle and orientation of the bevel, the depth of injection, and the quantity administered may vary. A linear threading technique, serial puncture injections, or a combination of the two have been used to achieve optimal results. If JUVÉDERM® Ultra injectable gel is injected too superficially, this may result in visible lumps and/or discoloration.
6. Inject JUVÉDERM® Ultra injectable gel applying even pressure on the plunger rod while slowly pulling the needle backward. The wrinkle should be lifted and eliminated by the end of the injection. It is important that the injection is 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.
7. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
8. The typical total volume of JUVÉDERM® Ultra injectable gel to achieve optimal correction is 1.6 mL per treatment site. The typical volume of JUVÉDERM® Ultra injectable gel to achieve optimal correction for repeat treatment is 0.7 mL per treatment site.

9. 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.
10. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color.
11. 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.
12. 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 to 2 weeks.
13. Patients may have mild to moderate injection-site responses, which typically resolve in a few days. If the treated area is swollen immediately after the injection, an ice pack can be applied to the site for a short period.
14. After the initial treatment, an additional treatment of JUVÉDERM® Ultra injectable gel (from 1 to 2 weeks later) may be necessary to achieve the desired level of correction. If the wrinkle needs further treatment, 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 wrinkle severity, skin elasticity, and dermal thickness at the treatment site.
15. The physician should instruct the patient to promptly report to her/him any evidence of problems possibly associated with the use of JUVÉDERM® Ultra injectable gel.

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

10. HOW SUPPLIED

JUVÉDERM® Ultra 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 nonpyrogenic. Do not resterilize. Do not use if package is opened or damaged.

11. STORAGE

JUVÉDERM® Ultra injectable gel should be stored at room temperature (up to 25°C/77°F). DO NOT FREEZE.

JUVÉDERM® Ultra 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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