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, nonpyrogenic, viscoelastic, clear, colorless, homogenized gel implant. It consists of cross-linked hyaluronic acid (HA) produced by *Streptococcus equi* 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).

## 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 trace amounts of 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 occlude the vessels and could cause infarction or embolization.
- 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 procedure reactions consist mainly of short-term inflammatory symptoms starting early after treatment and lasting ≤ 7 days' duration. 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.
- Based on preclinical studies, patients should be limited to 20 mL of JUVÉDERM® Ultra XC 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 facial wrinkles and folds (eg, lips) 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 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-lock and needle hub connection.

## 6. ADVERSE EVENTS

### A. Clinical Evaluation of JUVÉDERM® Ultra XC

A 2-week, randomized, controlled US clinical study for JUVÉDERM® Ultra XC and Ultra Plus XC compared with JUVÉDERM® Ultra and Ultra Plus without lidocaine showed a similar safety profile in all subjects (N = 72), with the exception of fewer reports of pain/tenderness with the product containing lidocaine. Common treatment-site responses (CTR), 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 Nasolabial Folds [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 CTR (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 injection-site response 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 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 injection-site response

**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 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 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. 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 (without lidocaine), which were not observed in the clinical trials; this includes reports received globally from all sources including scientific journals and voluntary reports. Adverse events with a frequency of 5 or more events are listed in order of prevalence: allergic reaction, blister, inflammation at the injection site, paresthesia, infection at the injection site, bleeding at the injection site, skin rash, malaise, headache, blanching, vision abnormalities, abscess at the injection site, urticaria, herpes simplex, telangiectasis, angioedema, flu-like symptoms, nausea, vascular event, dyspnea, dermatitis, granuloma at the injection site, and scar.

Vision abnormalities, almost all of which were nonserious events, have been reported in association with edema and overcorrection. The reported events consisted of blurred, double vision, or watery eyes and were noted after treatment of the tear trough region under the eyes. Time to onset ranged from immediate to 2 weeks postinjection. Interventions reported by physicians were noted to range from none to oral steroids to injectable hyaluronidase. Outcomes included resolved, improving, or ongoing at last contact.

Scarring has mostly been reported after treatment in the forehead or glabellar region and associated with a vascular event, necrosis, skin discoloration, blister, nodule, allergic reaction, and infection. Time to onset ranged from 2 weeks to 4 months. Interventions prescribed by the physicians included topical steroidal cream, nitropaste, oral steroids, and antibiotics. Additional treatments noted were a laser procedure and surgical scar revision.

Serious adverse events have infrequently been reported for JUVÉDERM® Ultra (reported with a frequency of 5 or more). The most commonly reported serious adverse events were edema, erythema, ecchymosis, pruritus, induration, and pain.

- The onset of edema generally varied from immediate to 2 weeks post-injection. The treatment prescribed included arnica, NSAIDs, antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, edema resolved within a day to a month.
- The onset of erythema generally varied from immediate to 1 week post-injection. The treatment prescribed included arnica, antihistamines, antibiotics, steroids, hyaluronidase, and laser treatment. In most cases, erythema resolved within 1 to 4 weeks.
- The onset of ecchymosis generally varied from immediate to 5 days post-injection. The treatment prescribed included arnica, NSAIDs, antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, ecchymosis resolved within 1 day to 4 weeks.
- The onset of pruritus generally varied from immediate to 1 week post-injection. The treatment prescribed included NSAIDs, antihistamines, antibiotics, and steroids. In most cases, pruritus resolved within 3 days to 2 months.
- The onset of induration generally varied from 1 day to 2 months post-injection. The treatment prescribed included antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, induration resolved within 1 week.
- The onset of pain generally varied from immediate to 8 days post-injection. The treatment prescribed included NSAIDs, antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, pain resolved within 1 to 6 weeks.

Additionally there have been reports of nodules, infection, allergic reaction, inflammation, abscess, deeper wrinkle/scar, and displacement.

- The onset of nodules generally varied from immediate to 2 weeks post-injection. The treatment prescribed included arnica, NSAIDs, antibiotics, steroids, hyaluronidase, and needle aspiration. In most cases, nodules resolved within 3 days to 1 month.
- The onset of infection generally varied from immediate to 1 week post-injection. The treatment prescribed included NSAIDs, antibiotics, and steroids. In most cases, infection resolved within 6 to10 days.
- The onset of allergic reaction generally varied from immediate to 2 months post-injection. The treatment prescribed included antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, allergic reactions resolved within 2 days to 4 months.
- The onset of inflammation generally varied from immediate to 2 weeks post-injection. The treatment prescribed included antihistamines, antibiotics, steroids, and hyaluronidase. In most cases, inflammation resolved within 3 days to 2 months.
- The onset of abscess generally varied from 2 days to 2 weeks post-injection. The treatment prescribed included antibiotics, steroids, and hyaluronidase. In most cases, abscess resolved within 4 to 6 weeks.
- The onset of deeper wrinkle/scar generally varied from immediate to 2 weeks post-injection. The treatment prescribed included antibiotics, steroids, and surgical correction of the scar. Deeper wrinkle/scar has been reported infrequently but more commonly after treatment in the glabellar region.
- The onset of displacement generally varied from immediate to 2 weeks post-injection. The treatment prescribed included antibiotics, steroids, hyaluronidase, and laser treatment.

## 7. CLINICAL STUDIES

### A. Pivotal Study for JUVÉDERM® Ultra (Without Lidocaine)

#### 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 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.

#### Study Endpoints

The primary effectiveness endpoint for the study was the IER's NLF severity score over the posttreatment 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, BOTOX® Cosmetic [onabotulinumtoxinA], microdermabrasion, or retinoic acid).

Subject demographics and pretreatment characteristics of the JUVÉDERM® Ultra effectiveness population are presented in Table 5.

**Table 5. 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 6.

**Table 6. 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 ($P < .0001$). 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 in 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 7.

**Table 7. 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 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 8.

**Table 8. 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

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 9.

**Table 9. 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 ($P < .0001$) than for the NLFs treated with JUVÉDERM® Ultra without lidocaine (Table 10) 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 11).

**Table 10. 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 11. 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). Mean baseline score was 2.3, and a clinically significant improvement (severity reduction) to 0.7 was observed after 2 weeks for both products.

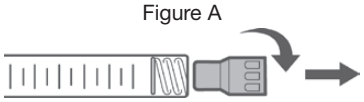
## 8. INSTRUCTIONS FOR USE

### 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-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.

Figure B

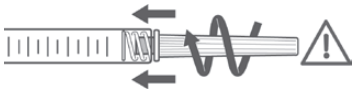


Figure C

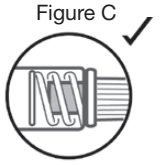
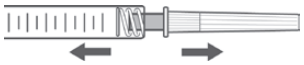


Figure D

**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. Physician Instructions

1. JUVÉDERM® Ultra XC injectable gel is a highly cross-linked 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, 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. Although the study showed JUVÉDERM® Ultra XC to be less painful than JUVÉDERM® Ultra, supplementary anesthesia may be used for additional pain management 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, depress the plunger rod until the product flows out of the needle.
5. 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.
6. The injection technique 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, or a combination of the 2 have been used to achieve optimal results. Injecting the product too superficially may result in visible lumps and/or discoloration.
7. Inject JUVÉDERM® Ultra XC by 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 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.
8. If the needle is blocked, do not increase the pressure on the plunger rod. Instead, stop the injection and replace the needle.
9. The typical total volume to achieve optimal correction of moderate to severe facial wrinkles and 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.
10. 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.
11. If immediate blanching occurs, the injection should be stopped and the area massaged until it returns to a normal color.
12. 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.
13. 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.
14. 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.
15. After the initial treatment, an additional treatment (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.
16. The physician 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 at 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 nonpyrogenic. Do not resterilize. Do not use if package is opened or damaged.

**10. STORAGE**

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.

**Manufactured by:**

ALLERGAN

Route de Proméry
Zone Artisanale de Pré-Mairy
74370 PRINGY-France

**Distributed by:**

ALLERGAN

Santa Barbara, CA 93111 USA
1-800-624-4261



**www.juvederm.com**
LDOC-02932 Rev.05