**JUVÉDERM® ULTRA PLUS 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 Plus 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 Plus 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 Plus XC is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.
   - JUVÉDERM® Ultra Plus XC contains trace amounts of Gram-positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.
   - JUVÉDERM® Ultra Plus 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 Plus XC into the vasculature may lead to embolization, occlusion of the vessels, ischemia, or infarction. Take extra care when injecting soft tissue fillers; for example, after insertion of the needle, and just before injection, the plunger rod can be withdrawn slightly to aspirate and verify the needle is not intravascular, inject the product slowly and apply the least amount of pressure necessary. Rare but serious adverse events associated with the intravascular injection of soft tissue fillers in the face have been reported and include temporary or permanent vision impairment, blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures. Immediately stop the injection if a patient exhibits any of the following symptoms, including changes in vision, signs of a stroke, blanching of the skin, or unusual pain during or shortly after the procedure. Patients should receive prompt medical attention and possibly evaluation by an appropriate health care practitioner specialist should an intravascular injection occur (see Health Care Professional Instructions #11).
   - 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 Plus 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 practitioners who have appropriate training, experience, and who are knowledgeable about the anatomy at and around the site of injection.
   - Health care professionals are encouraged to discuss all potential risks of soft-tissue injection with their patients prior to treatment and ensure that patients are aware of signs and symptoms of potential complications.
   - Based on preclinical studies, 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 (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 Plus 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 Plus 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 Plus 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 Plus 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 Plus 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 Plus XC were redness, swelling, tenderness, firmness, lumps/bumps, discoloration, and bruising.

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un satisfactory result, allergic reaction, skin discoloration, vascular occlusion, device malposition, and other symptoms such as increase or decrease in sensation, inflammatory nodule/ granuloma, derma tis, blister, dry skin, anxiety, overcorrection, necrosis, hyperpigmentation, hypopigmentation, edema, bruising, skin tenderness, and skin necrosis. Subjects were instructed to rate each common injection site response listed on the diary as “Mild,” “Moderate,” or “Severe.” A total of 146 subject NLFs were treated with the respective device (Table 2). Subject demographics and pretreatment characteristics of the subjects are reported in Table 14.

Delayed-onset inflammation near the site of dermal filler injection was one of the most commonly reported adverse events. 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 the Allergan Product Surveillance Department at 1-877-345-5372.

7. CLINICAL STUDIES

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

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

Up to 3 triplet 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, 26, 52, and 78 weeks after the last treatment. Standard 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 scale (0 to 4) photographic NLF severity scale. The subject made independent 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 scores and analyses included the subject’s and the Investigator’s live NLF severity assessments.

Subject Demographics

A total of 247 subjects, aged 26 to 74 years of age, were randomized and treated, and 140 (96%) completed the 6-month follow-up period. Prior to enrollment, 80 (55%) had previous experience with other dermal treatments (e.g., alpha-hydroxy acids, neuropeptides, microdermabrasion or retinol acid).

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

<table>
<thead>
<tr>
<th>NLF Severity</th>
<th>Number of Subjects</th>
<th>Baseline</th>
<th>Follow-up Week 4</th>
<th>Follow-up Week 12</th>
<th>Follow-up Week 24</th>
<th>Follow-up Week 36</th>
<th>Follow-up Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>8</td>
<td>9.3</td>
<td>9.4</td>
<td>9.5</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>12</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>III</td>
<td>20</td>
<td>20</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>IV</td>
<td>31</td>
<td>31</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>V</td>
<td>18</td>
<td>18</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>VI</td>
<td>2</td>
<td>2</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Mean Baseline NLF Severity Score:
- JUVÉDERM® Ultra Plus NLF: 2.6
- Zyplast® NLF: 2.6

NLF severity was rated on a 5-point scale from None (0) to Severe (5).

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

The primary effectiveness results for JUVÉDERM® Ultra Plus provided a clinically significant improvement in NLF severity (≥ 1-point mean improvement) with a large majority of subjects treated with JUVÉDERM® Ultra Plus demonstrating improvement at 24 weeks and beyond: 91% (21/23) at 24 weeks, and 90% (9/10) at 48 weeks (1 year).

C. Clinical Study for JUVÉDERM® Ultra Plus XC
A prospective, double-blind, randomized, within-subject, controlled multicenter clinical study was conducted to evaluate the safety and effectiveness of JUVÉDERM® Ultra Plus XC compared with JUVÉDERM® Ultra Plus 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 Plus XC in one NLF and JUVÉDERM® Ultra Plus without lidocaine in the other NLF. Within 30 minutes after all 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 at 24 weeks after treatment using the 5-point 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 (81%) of Caucasian descent (72%) with Fitzpatrick Skin Phototypes II or III (78%). Persons of color (Fitzpatrick Skin Phototypes IV, V, or VI) comprised 20% of treated subjects. Median age at study entry was 53 years (range, 32 to 80). Subject demographics are shown in Table 9.

Table 9. Subject Demographics (Number(%) of Subjects) N = 36 Subjects

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>27 (75%)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (25%)</td>
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</tbody>
</table>

Table 8. Follow-Up After Repeat Treatment Effectiveness Summary Investigator’s NLF Severity Scores

<table>
<thead>
<tr>
<th>NLF Severity</th>
<th>Improvement, Mean Improvement (≤ NLF = 146 NLFs)</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>–</td>
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<tr>
<td>II</td>
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<tr>
<td>III</td>
<td>–</td>
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<td>IV</td>
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<tr>
<td>V</td>
<td>–</td>
</tr>
<tr>
<td>VI</td>
<td>–</td>
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</tbody>
</table>

Throughout the 48-week follow-up period, JUVÉDERM® Ultra Plus provided a clinically significant improvement in NLF severity (≥ 1-point mean improvement) with a large majority of subjects treated with JUVÉDERM® Ultra Plus demonstrating improvement at 24 weeks and beyond: 91% (21/23) at 24 weeks, and 90% (9/10) at 48 weeks (1 year).

6. INSTRUCTIONS FOR USE

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 syringes 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.
**B. Health Care Professional Instructions**

1. JUVÉDERM® Ultra Plus XC injectable gel is a more highly cross-linked robust formulation, injected using a 27-G needle for volumizing and correction of deeper folds and wrinkles. 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 Plus XC to be less painful than JUVÉDERM® Ultra Plus, 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 Plus XC 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. 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

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 1-2 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 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 Plus 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 Plus XC injectable gel is supplied in individual treatment syringes with 27-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 Plus 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.

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