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Exhibit 1012
Prollenium v. Allergan

Injecting Puragen Plus into the Nasolabial Folds: Preliminary Observations of FDA Trial

Based on participation in ongoing FDA trials, the author presents his initial impressions of Puragen Plus for treatment of the nasolabial folds. Puragen and Puragen Plus (Mentor Corp., Santa Barbara, CA) are double-cross-linked NASHA products. Depending on double cross-linking for duration of effect, instead of a varying particle size, may allow for use of one filler at all levels in the soft tissue. Other features observed by the author in the clinical setting included reduced injection pain, minimal erythema and tenderness, typically 9 to 12 months' duration of effect, and high patient satisfaction. (*Aesthetic Surg J* 2006;26:741–748.)

Brian M. Kinney, MD, MSME, Los Angeles, CA, *is a board-certified plastic surgeon and an ASAPS member.*

In the United States, bovine collagen was essentially the only soft tissue filler on the market from the 1980s until just a few years ago. In many other countries, however, a wide variety of injectable materials have been long utilized for soft tissue filling.[1,2] Perhaps the most widely used substance today is polymerized chains of hyaluronan, hyaluronic acid (HA). Starting with the early 1996 Sweden experience, and spreading from Europe to the rest of the world, physicians have used cross-linked, non–animal source hyaluronic acid (NASHA).

A large body of NASHA clinical experience has grown with generally excellent results. In the November/December 1999 issue of *Aesthetic Surgery Journal*, Troilius[3] reported his initial favorable experience in more than 200 patients, using Restylane (QMed, Inc., Eatontown, NJ), a NASHA preparation (mean particle size 525 µ) single cross-linked with ether bonds by 1,4-butanediol diglycidyl ether (BDDE).

In December 2003, the Food and Drug Administration (FDA) approved Restylane, the first Restylane filler to be approved in the United States, and by January 2005, clinical use had become common. Advantages of Restylane include longer lasting effects than bovine collagen, improved contouring and volume augmentation, increased patient satisfaction, and freedom from allergy testing. A major disadvantage of many HA preparations is the pain associated with injection and the need for several different preparations based on particle size (300 to 650 µ) to allow for injection at various tissue depths. Additionally, while duration of effect is longer than with bovine collagen, it still falls short of ideal. Restylane Fine Lines is recommended for superficial use, Restylane for deeper use, and Restylane SubQ and/or Perlane are recommended for use deeper than the dermis. However, of these preparations, only Restylane is cleared for marketing in the United States. All of these products contain a concentration of 20 mg/mL.

Hylaform (Allergan Inc., Irvine, CA) uses single cross-linking by divinyl sulphone (DVS), has a mean particle size of 692 µ, and has not gained significant market share in the United States. Juvaderm (Allergan Inc., Irvine, CA), a higher-concentration NASHA preparation with a mean particle size of about 594 µ, was approved by the FDA in June 2006 and is just coming to market. A major stated claim is that Juvaderm is not a gel-particle suspension but, instead, a malleable smooth gel that flows more easily and with a higher level of control. There are several areas in which improved capabilities are desirable. Use of a single type of injectable at multiple tissue depths with only 1 syringe and 1 hypodermic skin puncture, little or no pain associated with the injection, and longer duration of effect are important advantages.

Materials and Methods

The half-life of non–cross-linked, naturally occurring hyaluronan in the body is 2 to 4 days, and about one third is turned over per day. Alteration of the physical and chemical properties is required for duration of effect in the soft tissues. In creating a synthetic analog, one can categorize at least 5 different types for HA products:

1. Liquid HA
2. Syrup-like HA with higher viscosity
3. A mix of syrup-like HA and weakly stabilized HA particles

4. A high concentration of HA particles with HA concentration of heavily cross-linked HA molecules. Puragen (Mentor Corp., Santa Barbara, CA) falls into this category.[5,6]
5. A high concentration of HA particles with high concentration of minimally modified HA molecules. The Restylane family of fillers falls into this category.

One method of increasing duration of effect is to vary particle size, as is demonstrated in the Restylane family. Another is to alter the chemistry of cross-linking by creating double-cross-linked chains with ether bonds and ester bonds. Puragen and Puragen Plus (Mentor Corp., Santa Barbara, CA) are double-cross-linked NASHA products. The ester bonds confer increased stability in vitro by resisting the enzymatic degradation by hyaluronidase and by protecting the ether bonds during sterilization. The ether bonds are hydrophobic and resist enzymatic degradation. The first chemical reaction is performed at high pH with 1, 2, 7, 8–diepoxyoctane (DEO), a hydrophobic epoxide that builds an HA network through ether bonds between hydroxyl groups. The second chemical low-pH reaction, using the same agent (DEO), further cross-links carboxyl groups to form ester bonds. The increased chemical stability allows for the addition of lidocaine 0.3% for a relatively pain-free injection. Enhanced stability in vivo and slower degradation in vitro are achieved by double cross-linking. Solid C13 nuclear magnetic resonance scanning in double-cross-linked HA shows a methylene bridge compared with standard HA.[5] The ester bond is confirmed by Fourier transform infrared spectrometry (FT-IR).[6]

Using a gel with a smaller average particle size (220 µ) may create a *smoother* injection (more continuous application of pressure). A gel with higher viscosity may require more pressure to inject. Depending on double cross-linking for duration of effect, instead of a varying particle size, may allow for use of 1 filler at all levels in the soft tissue.

Puragen Plus biocompatibility studies were performed, including skin sensitization in the guinea pig (no positive responses) and intradermal implantation in the guinea pig (minor initial reactions of erythema seen clinically and anti-inflammatory and giant cells seen on histopathology, minimal or undetectable at 27 weeks, similar to 2 comparator products). Also, there was no cytotoxicity in the Ames test at concentrations up to 5000 µg, no cytotoxicity in vitro in an agar overlay assay, no mutagenesis in vitro in a chromosomal aberration test, no unscheduled DNA synthesis in vitro, no pyrogenicity (ISO 10993-11), and no hemolysis. No necrosis, fibrosis, or granuloma were observed.

Puragen was introduced into the market in the European Union and many countries around the world in the spring of 2005. Its formulation is similar to Puragen Plus, except that it does not contain lidocaine. Puragen Plus has been undergoing FDA clinical trials since January 2005 in the United States. Each milliliter of Puragen Plus contains 20 mg of ether and ester cross-linked sodium hyaluronate 20 mg, sodium chloride 8.5 mg, disodium hydrogen orthophosphate dehydrate 0.22 mg, sodium dihydrogen phosphate dihydrate 0.045 mg, lidocaine HCl 0.3%, and water for injection.

FDA Clinical Trials

Five centers led by 3 dermatologists and 2 plastic surgeons participated in the original FDA clinical trials. In the original (first) study group, patients were randomized, Restylane was injected into one nasolabial fold (NLF), and Puragen Plus, into the other. None of the 5 centers had enough patients to reach statistical significance and results have been blinded from center to center.

In the continuing access (second) study, Puragen Plus was injected into both NLFs. Final data analysis has not been completed. Here, I report initial clinical impressions based on the experience of 1 center in the continuing access study. In future publications, I will present the compiled data. Study parameters included blood draw, photographs, 2 independent observers in the initial study, 1 observer (only) in the continuing access study, a pain assessment scale, and NLF scoring on a 6-part Lemperle scale. Follow-up took place at 14 days (when a second injection was allowed), and at 1, 4, 6, 9, and 12 months in the first study group and at 14 days, and 1, 6, 9, and 12 months in the second study group.

In the initial study group each patient wore an eye mask, and in both studies each patient was injected after a skin prep of alcohol only. For both studies, only patients with a Lemperle scale of 2 to 4 were allowed to participate. Exclusion criteria included severe skin disease (eg, eczema, psoriasis, severe acne, or rosacea), systemic diseases, history of NLF injection within 18 months, use of tretinoin within 4 weeks, use of botulinum toxin within 6 months, or laser resurfacing within 12 months. Blood was drawn at baseline, 30 days after the last injection, and at the 6-month visit.

Patients were injected in the NLF, deep and superficially, from the alar base inferior to the oral commissure as dictated by fold anatomy. In the first study group, 2 mL were allowed on each side during the first session,

Figure 1. A, *Pretreatment view of a 41-year-old woman.* **B,** *Posttreatment view 1 month following Puragen Plus injection into the nasolabial folds.* **C,** *Posttreatment view after 3 months.* **D,** *Posttreatment view after 6 months.* **E,** *Posttreatment view after 9 months.* **F,** *Posttreatment view after 1 year. (Patient had transient postinjection erythema that lasted from 1 to 2 days.)*

Figure 2. A, *Pretreatment view of a 39-year-old woman.* **B,** *Posttreatment view 1 month following Puragen Plus injection into the nasolabial folds.* **C,** *Posttreatment view after 3 months.* **D,** *Posttreatment view after 6 months.* **E,** *Posttreatment view after 9 months. The patient had deep folds; due to volume limitations she did not undergo complete correction in either fold; however, there is broad persistence of HA at 6 months.*

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