Fibroblast Injectable Gets Mixed Panel Review

BY ELIZABETH MECHCATIE

BETHESDA, MD. — A Food and Drug Administration advisory panel cast mixed votes on whether data on an injectable product derived from autologous fibroblast cells had demonstrated that it was safe and effective for treating moderate to severe nasolabial fold wrinkles in adults, the indication for which it is under review for approval.

At the meeting, the FDA's Cellular, Tissue and Gene Therapies Advisory Committee voted 11-3 that the data submitted by the manufacturer showed the product was effective in treating moderate to severe nasolabial fold wrinkles. Dr. Michael Olding, the panel's plastic surgeon and chief of plastic surgery at George Washington University, Washington, voted yes on the efficacy question, but emphasized that the indication was narrow and the product had not been shown to be effective in treating the nasolabial fold or contour deficiencies. He and the other panelists also said that they did not believe the agent had been shown to be effective in people over age 65 years, in nonwhite populations, or in older men, who were not well represented in the two pivotal trials. The efficacy had been seen primarily in white women under age 65 years, who accounted for most of the patients.

The panel also voted 8-6 that the data on the product, azfibrocel-T, had not demonstrated that it was safe for the indication, citing gaps in the data, including uncertainty over its mechanism of action and whether it induced scar formation or collagen production.

Other safety concerns included not knowing what happens to the fibroblasts over time and the lack of biopsies to help make that determination, as well as the lack of long-term data and the likelihood that, once approved, it would be widely used off-label, and there are no data to support other uses. The panel, however, did not appear overly concerned about the potential tumorigenicity of the product, although they said longer term data were needed to address this theoretical risk. The panel was not asked specifically whether to recommend approval.

The product, previously called Isolagen, was marketed commercially in the United States between 1995 and 1999 as a nonregulated product, and in the United Kingdom between 2002 and 2007. It is manufactured by Fibrocell Science Inc., which until August was Isolagen Technologies Inc. If approved, the product will be marketed as Laviv.

Azfibrocel-T is derived from fibroblasts obtained from three punch biopsies taken from behind the ear that are sent to a Fibrocell facility. Once there, they are isolated, harvested, prepared in an injectable cell suspension, frozen, and shipped to clinicians overnight, for use within 48 hours. The cells are harvested an average of 50 days after the biopsies, according to the company.

Treatment is administered in three doses at 5-week intervals and is injected with a 29-guage needle directly into the papillary dermis of the nasolabial fold wrinkles, where the fibroblasts "are believed to produce and organize extracellular matrix proteins, including collagen, by a mechanism analogous to natural wound healing," according to the company.

In the two pivotal, identical U.S. multicenter, double-blind trials, a total of 421 patients were randomized to receive three injections of azfibrocel-T or vehicle to the nasolabial fold wrinkles. Patients' mean age was 56 years, and most were white women.

At 6 months after the first treatment, significantly more of the patients who received the active treatment evaluated themselves as having a 2-point improvement in a 5-point scale evaluating the appearance of the "lower part of their face," when compared with those who had received the vehicle (57% and 46% of those who received azfibrocel-T in both studies, compared with 30% and 8%, respectively, among those in the vehicle groups). This was one of the two primary endpoints.

The second primary endpoint was a 2-point improvement on the Lemperle scale as assessed by a blinded evaluator's live assessment at the 6-month visit, using a photo guide of the scale. When enrolled, patients' wrinkles were at least a grade 3

(moderately deep) on the 6-point scale that ranges from 0 (no wrinkle) to 5.

The differences in evaluator assessments of the azfibrocel-T–treated patients and those who received the vehicle were not as wide as the patients' assessments, but were statistically significant. At 6 months, 33% of the patients in one study and 19% in the second study were evaluated as having a 2-point improvement, compared with 7% of those on the vehicle in both studies.

The most common adverse events associated with treatment were injection site reactions, namely erythema, swelling, bruising, and bleeding; these effects were mostly mild to moderate and did not last longer than 7-14 days. There was one case of a basal cell carcinoma near the injection site diagnosed 5 months after the third treatment. Clinical experience to date indicates the risk of scarring and keloids is minimal, according to the company, which has proposed plans for a mandatory physician training program.

Voting no on both efficacy and safety, panelist Dr. Lynn A. Drake of Harvard Medical School, Boston, said she was concerned about the lack of nonvisible evidence to support safety. She and other dermatologists on the panel said that it was important to determine whether normal or scar tissue was present after treatment, whether collagen was produced, and if so, what type, and whether elastin was affected.

Dr. Drake questioned whether the lack of efficacy in people over age 65 was indicative of the inability of the elderly to scar, and emphasized that once a new treatment for wrinkles becomes available, it is widely used immediately in all age groups and often in locations where it might not be safe.

If approved, azfibrocel-T would be the first cellular product for treating nasolabial fold wrinkles and the first fibroblast product contained in an injectable cell suspension, according to the FDA. It would be the second autologous cell product to be approved; the first is Carticel, a preparation of autologous chondrocytes used to repair knee cartilage. Clinical studies are underway in facial acne scars, gingival recession, and vocal fold scarring. A study in burn scars is being planned, the company said.

The FDA usually follows the recommendations of its advisory panels. ■