Trends-in-Medicine

November 2003

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Quick Pulse

Trends-in-Medicine
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FDA Panel to Consider Two Collagen Fillers

The FDA's General and Plastic Surgery Devices Panel is scheduled to review both Medicis' Restylane (non-animal hyaluronic acid) and Inamed's Hylaform (a hyaluronic acid-based dermal filler) on November 21, 2003. Based on interviews with six dermatologists including three Restylane researchers, the key Restylane issues are likely to be safety concerns.

The FDA is expected to ask panel members whether:

- It really is safe to use Restylane without skin tests.
- Bacterial protein issues with Restylane really have been resolved.
- There are safety issues related to the formaldehyde formed when the Restylane cross-links break down.
- Restylane completely breaks down in the body.
- Side effects such as inflammation, swelling, abscesses and nodules outweigh the benefits.

Sources all consider Restylane to be a relatively safe and effective injectable filler for facial wrinkles. A New York dermatologist said, "It's the No. 1 filler in the rest of the world. It's been used in Europe for many years, and in Canada for six years. It has basically replaced collagen across the world." A Florida dermatologist said, "I think that Restylane will be approved. It has been shown safe in Europe and Latin America."

Physicians had expected Restylane to be approved earlier this year, and they are puzzled as to why the FDA waited until November to schedule an advisory committee on Restylane. Sources wondered if FDA concerns about the safety of Artes Medical's Artecoll/Artefill might be weighing on Restylane. Artecoll/Artefill is a filler made up of 75% percent bovine collagen and 25% plexiglass (PMMA) beads, and there have been reports of granulomas with Artecoll/Artefill. The FDA's General and Plastic Surgery Devices Panel recommended approval of Artecoll in February 2003, but the FDA still has not approved it. A Florida doctor said, "I'm wondering whether the FDA is being very cautious because of concerns about Artecoll…My guess is that there has been some controversy around Artecoll since the panel recommendation. Since then, it has come out that there have been some foreign body reactions like lumpiness, and other things (with Artecoll)." A New York doctor said, "It's possible that the FDA is worried about the problems with Artecoll/Artefill. But the problems with Restylane have been very minor in comparison. And Restylane does get degraded, so it all goes away; it's not permanent…We were assuming that the FDA was going to approve Restylane last year, and then it kept getting pushed back for unclear reasons."

Doctors admitted that there have been some problems with Restylane, but sources described these problems as relatively minor. A Florida doctor expects the FDA panel to focus on Restylane's safety profile, commenting, "There will probably be a lot of safety questions." Among the safety concerns are:

- **Inflammation and abscesses.** A New York dermatologist said, "Everything can have a problem; you can always have some sort of inflammatory reaction to some component. There have been some inflammatory reactions with Restylane, and there have been some non-sterile abscesses. I know that Restylane Fine Lines is being reformulated. I guess they didn't like the way it flowed and some of the properties, so they are reformulating it a little bit. But in terms of comparing Restylane to the other fillers we've used, the problems have been certainly few and far between (with Restylane). I have a lot of patients waiting for it to be FDA-approved. I did one of the preliminary studies four or five years ago, and we liked it, and so did our patients." Another doctor said, "One thing the panel will probably want to know about is if the problems Restylane had in 1997 or 1999 have been fixed. They had a lot of bacterial protein in the product then, and there were inflammatory reactions to it. There were a lot of case reports about that. In 1999, I think, they reformulated the product to try to get the proteins out, so the panel will want to know if that worked."

- **Swelling and nodules.** A doctor said, "Swelling is an issue, and there have been reports of limp lip bump nodules. But I'm not sure of any specific issues. I don't think that there are any major issues because I can't think of any major problems with Restylane."

- **Allergic reactions.** A Florida doctor expects the FDA panel to focus on Restylane's safety profile: "There will probably be a lot of safety questions. They're going to want to make sure that the products don't need a skin test, first of all, and there is a lot of data to show that allergies are not a problem with Restylane. This is one of the first fillers that doesn't use a skin test."

- **Formaldehyde.** A source said, "The FDA will probably get into the issue of cross-linkers. Hyaluronic acid is a sugar, but if you inject the sugar into the skin, it only lasts about 12 hours. As a result, Restylane's sugar chains are hooked together, so that it looks like chicken wire. It's scaled cross-linking. The cross-linker breaks down into formaldehyde, and we know that can cause long-term problems, so I wouldn't be surprised if that question comes up."

- **Breakdown.** A doctor commented, "The panel will also probably want to know for sure if Restylane really breaks down 100% in your body, which it does. I think the FDA's primary concerns here are safety."

Restylane also may suffer somewhat at the panel by comparison to Inamed's Hylaform, which sources described as safer than Restylane. A doctor explained, "You don't get the inflammation and swelling with Hylaform that you get with Restylane. The swelling only lasts about a week with Restylane, but no swelling is better than some swelling…Restylane is a little more tightly cross-linked than Hylaform, so it's a little stiffer. The Restylane injection feels firmer in the skin, and it doesn't bind water quite as well as Hylaform does. Hylaform is less cross-linked, binds water better, and doesn't feel as stiff. Also, with Hylaform, the cross-linker doesn't turn into formaldehyde, so you don't get the swelling and inflammation you get from Restylane. Aside from that, they are very similar."

Medicis' marketing also may be an issue with the FDA, a source suggested. She said, "The Restylane people did a lot of marketing and advertising when they were not supposed to, and I'm wondering if the FDA is going to say something about that. I kind of believe that the FDA might have let Hylaform go before the FDA at the same time as Restylane as a sort of punishment because Restylane cheated a bit on the marketing side. I mean, they're talking about Restylane in every beauty magazine. Allergan didn't promote Botox illegally; word-of-mouth got the message out. I'm completely guessing here, but I find it very interesting that they'd allow Hylaform to go to panel at the same time as Restylane. Hylaform, in the opinion of a lot of doctors, is a better product, so maybe Medicis hurt itself by doing that."

The bottom line is that doctors in the U.S. are excited about Restylane, and they don't consider these "killer" issues for an FDA panel. However, it may be a more interesting panel than previously thought, and Hylaform may have an easier time with the panel than Restylane.

It also is interesting that the FDA decided to take two competing products to panel on the same day. This is reminiscent of the panels on consecutive days for:

- Transkaryotic Therapies' Replagal and Genzyme's Fabrizyme, two treatments for Fabry's Disease. The panel agreed that Fabrazyme was approvable one day, but the next day decided Replagal was not approvable.
- Novartis's Zelnorm (tegaserod) and GlaxoSmithKline's Lotronex (alosetron), treatments for irritable bowel syndrome. The panel recommend that Lotronex be allowed to return to the market after being pulled for safety concerns, but the next day got a positive reception at the panel, and the next day Zelnorm didn't.

Is there a message here for either Restylane or Hylaform? ♦