The Impact of Recent Regulatory Decisions Regarding the Iluvien Intravitreal Implant

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In this issue, Retina Today *introduces a new section that will feature a panel of thought leaders in the retina subspecialty who will discuss current and controversial issues in the field. For several years now, retina has been at the forefront of news in ophthalmology, and so there is no shortage of topics to address in this format.*

In this first installment, we focus on the recent decisions by the US Food and Drug Administration (FDA) and the European Union's (EU) Concerned Member States regarding the approval of Iluvien (Alimera Sciences), the injectable device that delivers sub-microgram levels of fluocinolone acetonide for up to 36 months (0.2 µg/day), for diabetic macular edema (DME).

In November 2011, the FDA stated that it was unable to approve a new drug application for Iluvien because the application did not provide sufficient data to support that Iluvien is safe and effective in the treatment of patients with DME. The FDA stated that the risks of adverse reactions shown for Iluvien in the FAME study were significant and were not offset by the benefits demonstrated by Iluvien in these clinical trials, according to an Alimera news release. In the complete response letter, the FDA indicated that Alimera would need to conduct 2 additional clinical trials to demonstrate that the product is safe and effective for the proposed indication. Alimera stated in a press release that 2 replicable trials of the same size would not be feasible to pursue.

Conversely, at the end of February of this year, Alimera announced the issuance of the Final Assessment Report from the Reference Member State (RMS), the Medicines and Healthcare products Regulatory Agency of the United Kingdom (MHRA), and the agreement of all the Concerned Member States that Iluvien is approvable. Since that time, Austria, Portugal, the United Kingdom, France, and Germany have granted marketing approval to Alimera for Iluvien.

To look deeper in to this issue, we invited Robert L. Avery, MD; David M. Brown, MD; and Baruch D. Kuppermann, MD, PhD, to provide their perspectives regarding Iluvien.

Retina Today: What are your thoughts on why the Iluvien did not receive FDA approval yet was deemed approvable in the European Union?

Dr. Kuppermann: The review processes are quite different in the United States and Europe. The European Medicines Agency (EMEA) relies much more heavily on key opinion leaders; this practice is somewhat frowned upon in the United States.

Many retina specialists in the United States were surprised by the FDA's nonapproval of the Iluvien because they met the primary efficacy endpoint in both clinical trials. It seems, however, that the FDA focused on the rates of cataract, which, although high (80%), came as little surprise to retina specialists, as we had expected this, and while not desirable, diabetics commonly develop cataracts. We were theoretically more concerned about the rates of glaucoma, as diabetics are not generally at high risk of glaucoma. However, the glaucoma surgical treatment rates with the Iluvien fluocinolone acetonide implant were much lower than we saw with the Retisert (fluocinolone acetonide 0.5 µg/day sustained delivery intravitreal implant for uveitis, Bausch + Lomb), with only 5% of patients treated with Iluvien needing surgical intervention for their glaucoma

compared with about 40% of patients treated with Retisert undergoing surgical glaucoma therapy. It should be noted that about 40% of Iluvien treated patients developed some intraocular pressure (IOP) rise requiring topical therapy.[1]

Of course, there were also secondary analyses looking at the duration of macular edema. Patients with duration of macular edema longer than 3 years benefitted most from the Iluvien compared with the standard of care for DME, which is laser.

So, it seems that the FDA had the option to approve it as a second line therapy for chronic DME and theoretically, could have avoided the cataract issue by approving it for pseudophakic eyes. Ultimately, most diabetics with chronic DME end up with cataracts at one point or another, so I think they could have captured a significant patient population that would be eligible for this product over time.

I think, in comparing the regulatory approaches in the United States and Europe, there is a more collaborative relationship between the government agencies responsible for device and drug approval and key opinion leaders built into the European process, whereas I don't think any of us who have experience with the Iluvien had an opportunity to call up the FDA and offer our input.

Dr. Brown: I practice in Texas where we have a huge population of diabetics who are underinsured. Because many patients have limited access to primary health care along with higher rates of obesity, DME represents a massive problem. Even if these patients had access to unlimited Lucentis (ranibizumab, Genentech), injections would be unable to control DME in many of these patients because the VEGF drive is so high in this disease and many don't have transportation or time off for monthly office visits.

My practice was a clinical site for the Iluvien trials, and I had several patients for whom 1 Iluvien fluocinolone acetonide implant insert controlled their DME for up to 2 years with no additional treatment. We certainly saw patients with increased IOP, and there was almost universal cataract progression in phakic eyes. I was, however, hopeful that the Iluvien fluocinolone acetonide implant might receive FDA approval with a restrictive label, such as for pseudophakic patients, or pseudophakic patients with chronic DME for more than 3 years. Many of these patients are already psuedophakic secondary to prior multiple injections of intravitreal triamcinolone. With the current FDA decision to require 3 additional 3-year trials, it is extremely unlikely that this therapy will ever be available for these end-stage patients. In my opinion, it is devastating that this device was not approved. I hope an appeal is possible.

Dr. Avery: I agree that it is disappointing that it could not have been approved with a restrictive label such as in pseudophakic eyes or in patients with edema for more than 3 years. These patients with chronic edema are often the hardest to treat with laser and yet, this group did the best with the implant in the clinical trials.

I am also a little disappointed that the FDA has not been more forthcoming with their rationale and has not provided more information on why they did not approve the implant based on the risk-benefit ratio. In my opinion, retina specialists should be allowed to practice our art of medicine, and there is clearly a subset of DME patients for whom this implant could be valuable. For instance, we might choose to use this implant in cases where we feel the risk-benefit ratio would be favorable such as with pseudophakic eyes with chronic edema. Or, we might choose to use the Iluvien for patients who have already undergone vitrectomy because off-label intravitreal anti-VEGF injections that we have at our disposal do not work well due to their decreased half-life in vitrectomized eyes. Additionally, it would be feasible to use this implant in eyes that have been tested for steroid response to minimize the risk of glaucoma.

Dr. Kuppermann: The reality is that we are already using triamcinolone acetonide off-label in our practices. In selected patients, steroids are one of our better treatment options for DME.

My practice in Orange County has many patients who have no or limited medical insurance and as a result, poor access to health care. I have found triamcinolone acetonide works well in these patients. First of all, ranibizumab is not yet approved for DME and in my mind, Avastin (bevacizumab, Genentech) does not seem to have the efficacy that was demonstrated by ranibizumab in the RISE, RIDE, and DRCR.net trials.[3,4]

That said, I would prefer to have option of the Iluvien at my disposal to have the benefits of the steroid effect with the balance of extended release.

I think the nonapproval of the Iluvien is unfortunate. The efficacy endpoint looked very good. The safety profile of cataract was something of an assumed endpoint and didn't really bother me that much. Of course, I would rather a therapy have no side effects, but given the need for treatment options in patients with chronic DME, even glaucoma rates observed with the Iluvien fluocinolone implant are manageable and certainly lower than that seen with the Retisert implant.

Dr. Brown: Regarding the approval of the Iluvien in the European Union, from what I understand, getting a CE mark is relatively easy. The funding or marketing approval country-by-country, however, is the more difficult process.

Dr. Kuppermann: This is correct. The EMEA approval is

just the beginning of the battle. In the United States, once FDA approval is granted, drugs and devices are paid for almost automatically, whereas in Europe, there are methods of comparative efficacy and cost assessments that vary.

Dr. Avery: One example of this is ranibizumab for DME in the United Kingdom. It was approved for DME in 2011, but it is not being paid for by the National Institute for Health and Clinical Excellence (NICE), so many hospitals are reported to be using bevacizumab. As a result, Novartis recently called for "judicial review" due to concerns regarding patient safety,[5] demonstrating that it is not as easy to use off-label medications in the European Union as it is in the United States. Thus, they are sort of "caught between a rock and a hard place" with DME, and it could be said that they have an even greater need for something like the Iluvien. The decision to approve the implant could have been in part based on this greater need.

Dr. Kuppermann: It is generally true that when there is an approved product for a specific indication in the European Union that off-label products are frowned upon. Some countries ban all off-label use, period.

The judicial review you reference is ironic because the BOLT study, which provided evidence to support that bevacizumab is effective for DME, came out of the United Kingdom.[6]

Going back to the situation in the United States, I am saddened that our treatment options for patients with DME have been limited by the nonapproval of the Iluvien. We are talking about a huge treatment burden to our patients and to our health care system, as this relatively young patient population with DME may well require monthly injections of ranibizumab for many years, if approved for DME by the FDA.

Dr. Brown: In terms of cost-effectiveness for the United States health care system, if the Iluvien implant was approved and covered (even considering the cost of cataract surgery and IOP management), it might prove to be less costly over time than continuous monthly ranibizumab injections.

Dr. Avery: It seems like the Iluvien would be a cost-effective treatment modality for those difficult patients with chronic CME who are unresponsive to laser or other treatment modalities, and I think more clarity as to why it was rejected would be welcomed by retina specialists.

Dr. Brown: Just recently, pSivida, who licenses its drug delivery technology to Alimera, announced that Alimera will have a chance to resubmit its application to the FDA (*See news story on page 11*). The details are not yet clear, but the speculation is that the focus will be on patients with chronic, refractory DME.

I am hoping that this appeal process does not require a new trial because I don't think that the resources exist for such a great expenditure. It would be like starting from scratch.

Dr. Kuppermann: I'll go one further to ask what a new trial could show that is different than what was demonstrated in FAME? Would it be feasible to test this device only in patients who are psuedophakic, as it seems that cataract formation was the main concern?

Dr. Brown: I understand that the FDA may have concerns that some clinicians may use the implant in patients in whom it might not be appropriate, but again, a restrictive labeling could have helped there. Unfortunately, there are probably too many patients with chronic DME to pursue orphan drug status.

Dr. Kuppermann: I believe that most in the retinal community are hopeful that the appeal process is productive because having the Iluvien available as a treatment option would be a great advantage for all of us and patients. ■

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