

OBR The Appeal of Genasense: The Drug, the Data, and the Tangled Web that its FDA Review has Become

by Jessica Wapner

Three years after its first review by the FDA, Genasense® may finally have the data to warrant approval in CLL. But will the regulatory powers-that-be agree? A look at the various factors at play in the saga that the Genasense review has become.

At some point—probably in the very near future—there will be a final decision by the U.S. Food and Drug Administration (FDA) about whether Genta's antisense agent Genasense (oblimersen sodium) will be approved for the treatment of relapsed/refractory chronic lymphocytic leukemia (CLL). In the meantime, the review process has become an increasingly tangled web of data, assertions, and upset. Many healthcare professionals feel that the drug warrants approval and that the FDA's treatment of Genasense has been too harsh. A look at what many feel has become a precedent-setting fiasco may provide some intriguing—and perhaps disconcerting—insights into the regulatory process and procedure.

Genta filed a New Drug Application for Genasense in December 2005, with the proposed indication being for the treatment of relapsed/refractory CLL. On September 6, 2006, an Oncology Drug Advisory Committee (ODAC), whose members are assembled by the FDA, met to consider the application. According to the data presented, Genasense combined with the standard chemotherapy regimen of fludarabine and cyclophosphamide (flu/cy) offered a 10 percent improvement in treatment outcomes compared with the chemo combination alone. However, citing several concerns, the ODAC members voted 7 to 3 against approval of the drug. The FDA followed the recommendation of the majority and rejected the application.

Among the concerns raised by the ODAC members was their preference for progression-free survival (PFS) as an endpoint. PFS, a secondary endpoint in the studies, was not superior for the Genasense arm, and has not yet proven to be so. Further, the benefit that was seen among patients treated with Genasense plus flu/cy was not con-

sidered to outweigh the associated increase in adverse events. The committee also asserted that the patients likely to benefit had not been clearly identified, and that the potential number of patients who would benefit did not warrant the approval of an expensive drug.

Shortly after that meeting, Genta held a teleconference with the FDA during which the agency agreed to consider additional information. But in December 2006, Genta received an informal communication from the FDA turning down the application.

According to Genta, and many CLL experts, the FDA's rejection of Genasense at that time was simply wrong. "I can't recall, as an oncologist, any time a [drug for a] highly unmet medical need that has a randomized trial with a high-quality regular approval endpoint meet that primary endpoint and is then rejected," says Genta CEO Raymond P. Warrell, Jr., MD.

Patients have voiced their concerns, too. "Here's another case of people who could be at death's door being denied a drug that may give more time and better health back to some of them. Don't we deserve to have it available?" wrote Andrew Schorr, of HealthTalk.com, a CLL survivor and host of the weekly Seattle-based radio program Patient Power. Schorr attended the ODAC meeting as one of the nonvoting open public hearing participants.

Genta announced its formal appeal of the FDA's decision in early 2007, and new data have been submitted to the FDA as part of that appeal. Recently presented at the 2007 annual meeting of the American Society of Hematology by Dr. Susan O'Brien and colleagues, the new data confirm that the complete remission seen among patients treated with Genasense plus flu/cy translates into improved survival compared with flu/cy alone.

According to these most recent findings (ASH abstract 751), which have been submitted to the FDA as part of the appeal, patients in the triple combination arm achieved a complete response (CR) rate of 17 percent, compared with

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a CR rate of 7 percent among patients treated with chemotherapy alone, a statistically significant difference.

“Exploratory analysis showed that [oblimersen]-treated patients survived significantly longer” the authors note in the ASH abstract, concluding, “These data strongly confirm that CR is a valuable primary endpoint for therapeutic trials in relapsed/refractory CLL and supports the clinical benefit associated with durable CR in this setting.”

The new data may be enough to warrant approval by the FDA. But the larger question of whether the agent should have been approved in the first place still looms, as do issues other than data that may have influenced the original decision.

First, the ODAC committee that met in September 2006 was slim on CLL expertise, with none of the 10 members specializing in this disease. On his widely read blog at Healthtalk.com, Schorr raised the point that others on the panel, whose expertise lay largely in the treatment of solid tumors, did not understand the particulars of treating CLL, such as the disease’s heterogeneity and the unmet medical need that Genasense could fill.

FDA representatives have noted the challenge of finding experts without conflicts of interest (COIs) to serve on ODAC panels and claimed that a panel of CLL experts that met the FDA’s COI policies could not be assembled. However, several of the panel members have been reported to have financial connections with competitors of Genta. This is not to say that those members voted out of bias, but the COI policy may have been applied inconsistently.

The FDA asserted that the patients who would benefit from Genasense were not clearly enough identified. But the study reviewed by ODAC in September 2006 was an intent-to-treat (ITT) analysis that met its primary endpoint. Further studies could certainly refine the target population, but that point is separate to the fact that the ITT trial met its primary ITT benefit. Genta has made clear to the FDA its intention to conduct Phase 4 trials, should the drug be approved.

According to publicly available summaries of the ODAC meeting, the data were not strong enough to warrant approval. However, it appears that an underlying reason for this assertion was a misunderstanding about what constitutes substantial evidence of efficacy and safety. “Typically, substantial evidence is statistical superiority in one or more controlled trials,” notes Dr. Warrell. “That was met in this trial.” During the appeal process, the FDA has conceded the point that this definition was not accurately conveyed to the voting ODAC members.

Regardless of the outcome, the saga of Genasense raises crucial questions about the FDA review process. These issues extend well beyond this one drug: as is widely known, the FDA review of Dendreon’s immunotherapy Provenge® is now under serious investigation. In its genuine efforts to ensure drug safety, is the FDA preventing drugs from reaching the patients who could be helped? Are there political reasons behind the FDA’s decisions to approve or reject drugs, and if so, what are they? Are drug applications such as these being used to set a precedent, rather than being evaluated for their own merit? Is the FDA weighing cost too heavily in its considerations of benefit?

Numerous CLL patients have already been helped by Genasense, and there is a clear desire among experts and patients alike that this drug be made available. At some point, the outcome of the Genasense application will be made clear. But its hard-to-treat side effects—the questions and issues raised during the review process—remain. **JW**

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We chose Genasense as an example of the regulatory difficulties that can be encountered when trying to get an oncology drug approved. We welcome your comments on this subject on our website at www.oncbiz.com.