Summary Minutes of the Oncologic Drugs Advisory Committee
September 6, 2006:

The summary minutes for the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee were approved on September 13, 2006.

I certify that I attended the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/	/s/
Johanna Clifford, M.Sc., RN Executive Secretary, ODAC	Maha Hussain, M.D., Acting Chair, ODAC

The meeting of the Oncologic Drugs Advisory Committee was held in the Maryland Ballroom, Hilton Washington DC/Silver Spring. Approximately 150 people were in attendance. The meeting was chaired by Maha Hussain, M.D.

The committee met to discuss new drug application (NDA) 21-874, proposed trade name Genasense ® (oblimersen sodium injection), Genta, Incorporated, with proposed indication for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Ronald Bukowski, M.D., Maha Hussain, M.D. (Chair), David Harrington, Ph.D., Pamela Haylock, M.D., Michael Perry, M.D., Maria Rodriguez, M.D.,

Oncologic Drugs Advisory Committee Consultants (voting):
Joao Ascensao, M.D., Ph.D.; Diane Mackinnon (patient representative); Michael Link, M.D., Gary Lyman, M.D., MPH.

Industry Representative (non-voting):
Antonio Grillo-Lopez, M.D.

Oncologic Drugs Advisory Committee Members Absent:
James Doroshow, M.D., S. Gail Eckhardt, M.D., Joanne Mortimer, M.D.

FDA Participants:
Richard Pazdur, M.D., Robert Justice, M.D, Ramzi Dagher, M.D., Robert Kane, M.D., Shenghui Tang, Ph.D.

Open Public Hearing Participants:
Andrew Schorr, Host and Founder, Patient Power, LLC; Chris Laudenslager; Laura Singer; Ruth Greenberg.

The agenda proceeded as follows:

Opening Comments	Richard Pazdur, M.D., Director Office of Oncology Drug Products, CDER, FDA
Sponsor Presentation	**Genta, Inc.**
Introduction	Loretta Itri, M.D. President, Pharmaceutical Development & Chief Medical Officer
Relapsed Refractory CLL	Michael Keating, M.D. Professor of Medicine M.D. Anderson Cancer Center
Clinical Efficacy/Safety	Loretta Itri, M.D.
Risk/Benefit	Susan O'Brien, M.D. Professor of Medicine M.D. Anderson Cancer Center

Conclusion	Loretta Itri, M.D.
FDA Presentation Genasense for the treatment of relapsed/refractory CLL in combination with fludarabine and cyclophosphamide	**NDA 21-874** Robert Kane, M.D., Medical Officer Division of Oncology Drug Products, OODP, FDA

Questions from the Committee

Open Public Hearing

Questions to the Committee

MEETING QUESTION

Background

For the approval of selected agents in acute leukemia, FDA has accepted durable complete remissions (CR) in single arm trials as evidence of clinical benefit. A substantial and durable CR rate in acute leukemia is generally associated with survival improvements and reductions in infections and blood product use.

In chronic lymphocytic leukemia, FDA has used the overall response category (CR + nPR + PR) to characterize the response rate for the therapies currently available. For the 1991 approval of Fludara, the objective response rates (ORRs) in two trials were 32% and 48% with response durations of 1.25 and 1.75 years, respectively. These responses were associated with improvements in hemoglobin and platelet counts substantiating clinical benefit. For the 2001 accelerated approval of Campath, ORRs in three trials were 33%, 21%, and 29% with response durations of 7, 7, and 11 months. All of the above response rates reflect the single-agent activity of the study drug. For randomized trials conducted in this setting, the FDA has recommended to sponsors that either time-to-progression (TTP) or progression-free survival (PFS) be used as the primary endpoint. The FDA believes that a statistically significant, clinically meaningful improvement in TTP or PFS would constitute clinical benefit leading to regular approval in CLL.

In contrast to the above approvals where single-agent activity was demonstrated in single arm trials, the applicant has provided a randomized "add-on" trial adding Genasense to fludarabine plus cyclophosphamide. This randomized trial allows us to examine not only response rate (both CR and ORR), but also allows analyses of TTP and survival and more accurately characterizes Genasense's adverse event profile. More importantly, the study allows us to isolate the contribution of Genasense to response rate. When the response analysis is limited to the CR plus nPR rate, the addition of Genasense to fludarabine/cyclophosphamide resulted in a 10% difference (17% for the Genasense-containing arm vs. 7% for the control arm of fludarabine/cyclophosphamide, $p = 0.025$). However, when response is defined as CR plus nPR plus PR, no improvement was demonstrated with the addition of Genasense (41% vs. 45%). There was no improvement in overall response duration, TTP, survival, or in any other planned secondary analyses. The composite endpoint of "symptom-free time" presented by the applicant should be considered exploratory. The clinical trial was not blinded, the analysis was not pre-specified, and the symptom-free time was calculated by adding discontinuous times.

The addition of Genasense to the fludarabine plus cyclophosphamide regimen is associated with increased toxicities, including increased numbers of severe AEs and serious AEs and more nausea, vomiting, fever, fatigue, blood transfusions, and bleeding. Genasense administration requires an indwelling central venous access device for continuous intravenous infusion and an external infusion pump (or hospitalization) for 7 days monthly. Infusion catheter-related complications occurred in 16% of the Genasense patients, including catheter infections and venous thromboses, compared to a 3% rate in the control arm.

Genasense ODAC Question

The Applicant has requested the Agency to consider the current application under the accelerated approval regulations. Although the primary endpoint may differ, both approval types should have substantial evidence of safety and efficacy demonstrated in adequate and well controlled trials (plurality indicating multiple trials). Under accelerated approval regulations, the Agency may grant approval based on a surrogate endpoint "reasonably likely" to predict clinical benefit. Based on the mature data from this study, the FDA believes that accelerated approval is problematic since the difference in response rate (CR + nPR) in this single completed, randomized study did not predict an improvement in TTP or provide other evidence of clinical benefit. In accepting single trials for oncology approvals, the Agency has relied on secondary endpoints to provide corroborating efficacy evidence. The addition of Genasense to fludarabine plus cyclophosphamide did not improve secondary endpoints (ORR, TTP, clinical benefit elements). Although the primary endpoint analysis was statistically significant, the clinical significance of this 10% improvement in complete plus nodular PR rate must be viewed in both a risk/benefit analysis and in the context of the totality of evidence available at the time of approval.

1. **VOTE: Does this single study, with a 10% improvement in CR plus nPR rate but no demonstrated improvement in overall response rate (CR + nPR + PR), time-to-progression, survival, or symptomatic benefits between the two study arms, demonstrate substantial evidence of effectiveness for Genasense in this CLL population?**

Vote: ***Yes = 3*** ***No = 7***

Comments:

The committee overall agreed that the study did not demonstrate "substantial" evidence of effectiveness. Although, some felt that the drug could potentially display some evidence of effectiveness in other settings, they agreed that the trial did not result in "substantial" evidence of effectiveness in this population, as defined in the question.

Several ODAC members expressed concern that the population likely to benefit from Genasense has not been adequately characterized. For Example, no data was provided regarding the Bcl-2 status of patients enrolled to the randomized trial or any effect of Genasense on Bcl-2 in these CLL patients.

They further felt that the data did not present compelling evidence in the endpoints of TTP or OS or symptomatic improvement indicating clinical benefit and that the data presented lacked the ability to show with some likelihood, who would respond to the drug. Additional concerns from the committee were noted in regard to the doubling of serious adverse events with the administration of the product.

The meeting adjourned at approximately 12:00 noon.