Food and Drug Administration
Center for Drug Evaluation and Research

Arthritis Advisory Committee
Silver Spring Holiday Inn, 8777 Georgia Avenue, Silver Spring , MD

Questions
March 4, 2003
Safety update on the TNF-α inhibitors

Lymphomas and other Malignancies

1. Please comment on the characteristics of the cases of lymphomas (e.g., age at time of diagnosis, distribution of NHL vs. HD, histology, etc.) observed in patients treated with TNF inhibitors relative to the experience in the general population and relative to the experience in people with underlying RA or Crohn's Disease.

2. Please discuss the strength of the available evidence (including the pre-marketing controlled trial experience, open label extension studies, post-marketing registry data, and post-marketing spontaneous reports, incidence rates over time, etc.) and any conclusions you are able to draw regarding an association between TNF-blocking treatments and lymphoma.

3. As part of post marketing studies, all 3 manufacturers have committed to follow between 1000 and 2000 patients with RA and to provide the agency with updated information on malignancies annually for a minimum of 5 years. At 5 years, the agency will determine whether additional follow up will be necessary. The yearly update includes numbers and types of tumors, based on histology and other standard assessments.

4. Should the companies be asked to obtain additional specific types of information not normally assessed in patient management that could help elucidate the relationship between anti-TNF therapy and lymphoma? What findings would suggest that there be continued active follow up of this nature?

5. Please discuss how best to communicate information about lymphomas to health care providers and patients. For each of the respective product labels, please discuss how the agency should present the data on the observed incidence of lymphoma, the degree to which the data suggest an association, and the degree of uncertainty about the association. Should the standardized incidence ratio (SIR) with respect to the general population be presented? Should the SIR with respect to the RA population be presented? Should the labels be similar for each product?

6. Please comment on the incidence and types of other malignancies observed in the clinical trial and post-marketing experience with the TNF blocking agents. Do these data raise any concerns at the present time?

Other safety data

1. Please comment on the data observed in the randomized controlled trials in patients with New York Heart Association class III and IV heart failure as well as the spontaneous reports of adverse cardiac events in patients with RA. Is it reasonable to discuss CHF related safety concerns in labels for all TNF blocking agents? Other than product label changes that will caution use in patients with pre-existing CHF or who develop CHF while on treatment, should the companies be asked to develop additional procedures for CHF risk management?

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2. Please comment on any other concerns based on the safety updates provided and any specific actions the agency and the various companies should undertake to address them.