FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Arthritis Advisory Committee

September 6, 2005

Questions to the Committee

1. There are 3 randomized placebo controlled studies of Abatacept in rheumatoid arthritis patients that evaluated the proposed weight-tiered dosing regimen and two studies which evaluated a regimen of 10 mg/kg. One study examined monotherapy with Abatacept, and 4 studies examined Abatacept as an add-on to other products.

   Three of these studies followed the FDA Guidance on Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis as it relates to the duration of the placebo controlled period and the nature of the endpoints. Compared to placebo, Abatacept treatment showed effects on signs and symptoms (e.g., as evaluated by the ACR criteria), radiographic progression (as evaluated by the total Sharp Score) and physical function (as evaluated by the HAQ-DI) have been observed.

   Please discuss the strength of evidence regarding the demonstration of efficacy of Abatacept in the treatment of patients with rheumatoid arthritis.

   Several potential safety concerns have been identified for Abatacept:

   For each of the following (Topics 2-6) please discuss the safety profile of Abatacept, and the major concerns you believe may be present. Please identify the areas of concern for which further safety assessment is warranted, and the types of studies that should be conducted to further characterize these concerns.

2. More serious infections have been observed in the Abatacept-treated groups than in the control comparison groups. This was particularly notable for, but not limited to, patients who received concomitant TNF-antagonist agents.

3. The Abatacept clinical development program incorporated an analysis of "Infections of Special Interest", which included fungal (e.g. aspergillosis), viral (e.g. herpes zoster) and bacterial infections (e.g. pneumonia and TB). Overall Infections of Special Interest were observed in 10% of Abatacept-treated patients compared to 7% of control group patients, with the majority of this difference in the Herpes and Pneumonia categories. However the total patient sample size and exposure duration (median 14 months) cannot rule out an Abatacept-associated increase in the rate of uncommon opportunistic infections.

4. Overall malignancy rates were not substantially different between Abatacept and placebo treated patients (1.5% and 1.1% respectively). However, more cases of lung cancer were observed in Abatacept treated patients than in the control group (4 versus 0). The rate of lymphomas was not increased in Abatacept-treated patients compared to placebo-treated patients, however for the complete safety dataset (controlled and uncontrolled periods) the rate of lymphoma in Abatacept-treated patients was higher than expected based on the general US population. In addition, an increase in the rate of lymphomas and mammary tumors was observed in the murine model, though not in non-human primates.

5. Hypersensitivity reactions have been observed, including a case of anaphylaxis.

6. Patients with chronic obstructive pulmonary disease (COPD) treated with Abatacept had a higher incidence of adverse events and serious adverse events, particularly respiratory disorders.

7. Please discuss any other areas of safety concern that have not been specifically highlighted above.

Overall Assessment

8. In view of all the data available for the safety and efficacy of Abatacept, do the benefits outweigh the known and potential risks?

   Please discuss and then vote.

Additional Advice

9. In addition to assessing ACR 20, 50 and 70 responses, the sponsor collected data on the percentage of patients achieving low disease activity, as assessed by the DAS-defined remission (DAS < 2.6). Since DAS is a composite of tender joints, swollen joints, pain and acute phase reactants, it is possible to achieve a DAS below 2.6 but still have multiple tender and/or swollen joints.

   a. Does assessing the proportion of patients achieving low disease activity provide important information of a nature that is not adequately assessed by analyzing the proportions of patients achieving high levels of improvement (e.g. ACR 70 or major clinical response). If so, please discuss the nature of difference in the information

   b. If assessing the proportion of patients achieving low disease activity does provide important additional information, please comment on which measures are suitable or optimal to identify low disease activity. Please consider in particular:

      i. DAS-defined remission (DAS < 2.6);

      ii. DAS < 2.6 plus no more than 1 tender joint;

      iii. DAS < 2.6 plus no more than 1 tender or 1 swollen joint