

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Arthritis Advisory Committee
Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD**

**Questions
August 16, 2001
BLA STN 103950 Kineret™, (anakinra), Amgen, Inc.**

SAFETY (in absence of TNF agents)

Patients receiving anakinra in the absence of anti-TNF blocking agents experienced a 3 fold higher rate of leukopenia across all studies (12% anakinra, [95% CI 9.9-15%] vs 5% placebo, [95% CI 2.5-9.2%]), a higher rate of serious infections in one study (2.1% anakinra [95% CI 1.3%-3.1%] vs. 0.4% placebo [95% CI .01-2.0%]), and, frequently, injection site reactions. Although nearly 2000 patients have been treated with anakinra, only 175 have received the product for one year or longer.

Please discuss these safety data, particularly with regard to:

- 1) the size of the safety database. Has the sponsor studied an adequate number of patients to support the safety of anakinra for the treatment of rheumatoid arthritis?
- 2) the incidence of leukopenia. Were anakinra to be approved, what precautions or guidance should be included in the package insert for the monitoring of leukopenia?
- 3) the risk of serious infection with use of anakinra in the absence of anti-TNF blocking agents. Are additional studies needed to further characterize this risk? If so, what types of studies should be conducted?

EFFICACY AND SAFETY

Anakinra was shown to provide higher ACR 20 response rates than placebo in a large randomized controlled trial (38% vs. 27% respectively, $p < 0.01$). Clinical data from other smaller randomized studies was also supportive of the clinical efficacy of anakinra. Relatively few patients experienced ACR 50 responses (17% anakinra vs. 8% placebo) or ACR 70 responses (14% vs. 5%), however.

4. Please discuss the efficacy data, particularly with regard to the relatively few ACR 50 and ACR 70 responses when compared to placebo. Given the overall benefit (absolute 10-15% higher ACR 20 response rates compared with placebo and smaller amounts of difference with regard to ACR50 and 70) and a potential increased risk of serious infection (5-fold in one study), do these data demonstrate an appropriate safety and efficacy profile of anakinra for approval as a treatment for rheumatoid arthritis?

USE IN COMBINATION WITH OTHER IMMUNOMODULATORY AGENTS

It is likely that anakinra will sometimes be used in combination with other therapeutic agents, including anti-TNF agents. Safety data for the combination of anakinra with etanercept are very limited. Data from one small open-label study showed a relatively high rate of patient withdrawal from study (21/58) and serious adverse events (7/59), including four serious infections.

Please discuss these safety data:

- 5) Were anakinra to be approved, what types of contraindications, warnings, precautions or guidance should be given in the package insert regarding the use of anakinra with other immunomodulatory therapies, especially anti-TNF agents?
- 6) Were anakinra to be approved, what types of additional studies should the sponsor conduct to better characterize the safety (and efficacy) of anakinra when used with other immunomodulatory therapies, especially anti-TNF agents?

PEDIATRIC STUDIES

The December 1998 Regulations require studies in pediatric patients if the drug or biological therapy that is or will be marketed for adults is likely to be used in substantial number of pediatric patients or represents a meaningful therapeutic advance. Anakinra has not yet been studied in pediatric patients. Etanercept is licensed for pediatric patients (as young as 4 years of age) with polyarticular onset JRA, a long term registry is underway, and studies are in progress in patients with other forms of JRA. Remicade is also being studied in pediatric patients with JRA.

7. If Anakinra is licensed, should the company be required to conduct studies in pediatric patients as per the 1998 regulations?