Food and Drug Administration
Center for Drug Evaluation and Research
Arthritis Advisory Committee
Silver Spring Holiday Inn, 8777 Georgia Avenue, Silver Spring, MD
March 5, 2003
Questions
NDA: 20-905, ARAVA™, (leflunomide), Aventis Pharmaceuticals, Inc.

Efficacy

The "Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)" released in February 1999, includes the recommendations for the claim "Prevention of Disability". As noted in this guidance, "Studies should be two to five years in duration" to support this claim. Recent studies attempting to assess efficacy and durability based on placebo-controlled or add-on-therapy studies have identified limitations for proper conduct and interpretation of these studies, because of high withdrawal rates. Therefore, FDA is considering a revision of this claim.

The Health Assessment Questionnaire (HAQ) has been evaluated in a variety of clinical trials and settings over the years, particularly for physical function in activities of daily living. It is recognized in the RA guidance document as an adequately validated measure for use as the primary outcome measure in trials of physical function in rheumatoid arthritis.

1. In light of the available literature on the HAQ instrument:

    a) Does the term "physical function" or "disability" better capture the clinically relevant information ascertained in this instrument?

    b) Are the more recent derivatives such as the Modified Health Assessment Questionnaire (MHAQ) and the Multidimensional Heath Assessment Questionnaire (MDHAQ) appropriate and validated endpoints and substitutes for the HAQ in this regard?

For this meeting, the committee has been provided data evaluating the effects of leflunomide on physical function from clinical studies including data at 12 and 24 months timepoints. The effects of patient withdrawals on Last Observation Carried Forward (LOCF) landmark analyses of an Intent to Treat (ITT) population at these timepoints has been discussed. The current guidance notes that "studies should be 2-5 years in duration". Advisory committee deliberations in 1998 concluded that the controlled data at one year demonstrated improvement in physical function. Similar one-year controlled data, along with durability of response during the second year in those patients who responded at one year, have been used to support approval of one therapy for improvement in physical function (infliximab).

2. For the domain of disability or physical function, what duration of a superiority study (placebo or active comparator) is needed to robustly identify an improvement?

3. What type of data are needed to assess durability of effect beyond an initial superiority study period? Examples might include:

    a) maintenance of effect size compared to baseline seen during initial superiority study period in ITT
    b) maintenance of effect size compared to baseline superiority study period only in responders during initial treatment period
    c) maintenance of effect size compared to end of superiority study period (ITT or responders).

4. Are the data on leflunomide presented by the sponsor adequately robust (effect size and robustness of database) to support labeling for "improvement in physical function"?

Safety

In the context of the strengths and weaknesses of available evidence presented in the briefing documents and here today, including that from controlled clinical trials, open label studies, post-marketing spontaneous reports, etc., and conclusions that you are able to draw regarding an association between leflunomide and serious hepatotoxicity, please address the following questions:

1. Considering the universe of available disease modifying therapies, is the benefit-to-risk profile for leflunomide acceptable for current indications?

    a) reduce signs and symptoms of rheumatoid arthritis
    b) retard structural damage as evidenced by x-ray erosions and joint space narrowing

2. If the answer to #1 is yes, what, if any, labeling, other risk communication and/or risk management is warranted for the optimal safe use of leflunomide?