

Discussion and Consideration of Proposed Radiographic Outcome Measures for Investigational Agents for the Treatment of Rheumatoid Arthritis

Briefing Document for Arthritis Advisory Committee Afternoon of July 12th, 2000

Purpose: To begin a discussion with the committee about a) claims for *prevention* of structural damage and b) the usefulness of measuring other structural outcomes not listed in agency guidance documents, including *reduction* or *healing* of erosions.

Background: The document entitled “Guidance for Industry: Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA), February 1999” addresses potential claims for the treatment of RA. Among these is *prevention of structural damage*. Examples are provided in the guidance document of outcome measures that could support a prevention of structural damage claim. They include:

1. “Slowing X-ray progression--using either the Larsen, the modified Sharp, or other validated radiographic index”.
2. “Prevention of new X-ray erosions--maintaining an erosion free state or preventing new erosions.”

The document adds that “because slowing of radiographic progression does not in itself define a patient benefit, it is expected that the claim of prevention of structural damage would be submitted for an agent that has been shown (previously or concomitantly) to be effective for one of the other claims (e.g. prevention of disability). It also states that “...the ultimate goals of slowing joint destruction are to improve symptoms and to preserve functional ability. Therefore, slowing radiographic progressions of disease is considered a surrogate marker for overall patient benefit in RA. ”

Finally, in the context of accelerated approval, the document states “One example of a significant effect on radiographic progression might be the demonstration, in a randomized controlled trial, of maintenance of an erosion-free state in a large majority of treated patients when control patients develop multiple erosions...The use of the *accelerated approval* pathway would necessitate timely completion of phase 4 studies using acceptable clinical endpoints evaluating signs and symptoms or prevention of disability.”

Since the guidance issued, a number of products have been studied in clinical trials in which radiographic outcomes, as well as clinical outcomes, were assessed. Two of these products are labeled for improving structural outcomes. In addition to showing a beneficial effect on signs and symptoms, leflunomide (Arava) is indicated “to retard structural damage as evidenced by X-ray erosions and joint space narrowing” and etanercept (Enbrel) for “delaying structural damage in patients with moderately to severely active rheumatoid arthritis” Note that neither of these products is specifically indicated for *prevention of structural damage*.

Sponsors have now sought advice from the agency about the type of data required to allow claims of *prevention of structural damage*. In addition, sponsors are interested in pursuing other claims not included in the guidance document, including *reduction* or *complete healing* of [existing] erosions. The agency seeks this committee's input as to how to advise sponsors, given uncertainties about how best to define *prevention of structural damage* and the absence of established methodologies to study erosion healing.

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

July 12, 2000

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Questions to the Committee:

- 1) The agency's guidance document for sponsors developing therapeutic agents to treat rheumatoid arthritis lists a claim for *prevention of structural damage*. Sponsors pursuing this claim must conduct a study of at least one year in duration. Two agents recently approved by the agency showed effects on radiographic progression in patients treated for one year. These products are indicated for *retarding* or *delaying* structural damage and not for *preventing* structural damage, however, since many patients were observed to have worsened structural damage on treatment. In this context a *prevention* claim seemed inappropriate.
 - a) **Is *prevention of structural damage* a viable claim in RA given that, even following treatment with very active agents, some patients are likely to have some evidence some disease progression?**

If yes:

- b) **Please comment on criteria that could be used to label a product for *prevention* of structural damage. Are data from trials of one year duration adequate for this claim, or should data on longer-term effects be collected before such a claim is considered? Are there criteria available to select patient populations who are likely, without treatment, to develop erosions? If so, which ones? Should there be a minimum proportion of patients who do not show progression before such a claim is given?**
- 2) There is considerable interest by sponsors to pursue claims not listed in the agency guidance document. These include reduction or elimination (healing) of erosions. The agency seeks input from the committee about whether and/or how such claims should be pursued.
 - a) **Is a *reduction in number of existing erosions* a viable claim in RA?**

If yes:

- b) **Please discuss ways in which these outcomes could be measured (e.g., which imaging modalities, duration of study to determine durability of effect, etc). Is there a minimum # of erosions (compared to baseline) that should be healed in order to consider a product reasonably likely to confer clinical benefit?**

