Summary Minutes of the
Arthritis Advisory Committee
July 29, 2008
Location: Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the July 29, 2008 Meeting of the Arthritis Advisory Committee of the Food and Drug Administration were approved on _8/15/2008_____

I certify that I attended the July 29, 2008 meeting of the Arthritis Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/_____
Nicole Vesely, Pharm.D.
Designated Federal Official, AAC

_____/s/_____
H. James Williams, M.D.
Acting Committee Chair

Meeting of the Arthritis Advisory Committee
July 29, 2008

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 29, 2008 at the Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by H. James Williams, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 225 persons in attendance. There were (2) speakers for the Open Public Hearing session.

Issue: The committee will discuss biologics license application (BLA) 125276, ACTEMRA (tocilizumab), Hoffmann-La Roche, Inc., for the proposed treatment of adult patients with moderately to severely active rheumatoid arthritis.

Attendance:
Arthritis Advisory Committee Members Present (Voting):
Diane Aronson (Consumer Representative), Christy Sandborg, M.D., Robert Stine, Ph.D., Dennis Turk, Ph.D.

Special Government Employee Consultants (Temporary Voting Members):
David Blumenthal, M.D., H. James Williams, M.D. (Acting Chair), David Pisetsky, M.D., Ph.D., Gary Hoffman, M.D., M.S., David Felson, M.D., MPH, Michael Weisman, M.D., Leona Malone, LCSW (Patient Representative)

Non-voting Participant:
Mark Fletcher, M.D. (Industry Representative)

Arthritis Advisory Committee Members Not Present:
Gail Kerr, M.D.
Kenneth Saag, M.D.
Nancy Olsen, M.D.

FDA Participants (Non-Voting):
Curtis Rosebraugh, M.D., Bob Rappaport, M.D., Jeffrey Siegel, M.D., Sarah Okada, M.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Susan Karder
Phylicia Melugian

The agenda was as follows:

Call to Order and Introductions	**H. James Williams, M.D.** Acting Committee Chair Arthritis Advisory Committee
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official
Opening Remarks	**Jeffrey Siegel, M.D.** Clinical Team Leader, Division of Anesthesia, Analgesia and Rheumatology Products, CDER/FDA

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Sponsor Presentation Introduction/Overview	**Hoffmann-La Roche, Inc.** **Jonathan Leff, M.D.** Vice President and Clinical Development Head Inflammation Disease Biology Area
Efficacy	**Kenneth Bahrt, M.D.** Global Medical Director, Autoimmunity
Safety	**Joel Krasnow, M.D.** Clinical Science Leader
Risk Mitigation/ Pharmacovigilance	**Philippe Van der Auwera, M.D., Ph.D.** Global Head of Drug Safety
Summary	**Kenneth Bahrt, M.D.** Global Medical Director, Autoimmunity

Questions from the Committee to the Sponsor

FDA Presentation Actemra (tocilizumab) for Rheumatoid Arthritis: FDA Perspective	**BLA 125276** **Sarah Okada, M.D.** Clinical Team Leader, Division of Anesthesia, Analgesia and Rheumatology Products, CDER/FDA

Questions from the Committee to the FDA

Open Public Hearing

Questions to the AAC
and AAC Discussion

Adjourn

Questions to the committee:

1. **Safety of Tocilizumab**

   The FDA has identified the following adverse events observed in the tocilizumab clinical development program as being of potential concern:

   - Serious infections
   - Liver enzyme abnormalities and lipid parameter changes
   - Gastrointestinal tract perforations
   - Demyelinating disorders

   Please discuss:

   a. the clinical impact of these adverse events in the patient population
   b. the need for monitoring
   c. the impact of these adverse events on the selection of appropriate patients for treatment

Serious Infections

Committee members felt there was a lack of data in those patients greater than 75 years old and those patients with COPD.

Liver Enzyme Abnormalities

The committee discussed appropriate monitoring for this adverse event. The committee agreed that regular monitoring of liver enzymes was necessary until further information was made available to determine the frequency of this monitoring. One member recommended monitoring every 8 weeks.

Lipid Parameter Changes

One member noted that a warning should be placed in the label due to the lipid parameter changes. Other members felt that the elevations weren't high enough to add a warning to the label. Members felt that using surrogate markers to detect CVD may not be predictive without a larger trial to study endpoints. Members disagreed over whether monitoring should be done as was put forth by the sponsor or if further monitoring beyond the sponsor's proposal was needed.

Gastrointestinal Tract Perforations

Members questioned if the mechanism of action of tocilizumab could have a relationship to GI perforation. Members were concerned with the combination of tocilizumab and NSAIDs or corticosteroids and felt that more data was necessary to determine the risk of these combinations.

Demyelinating Disorders

Committee members felt they needed data on the background rate of demyelinating disorders in RA.

Please see the transcript for detailed discussion.

2. **Appropriate Dosing**

   Three of the five studies submitted in the application contained data on tocilizumab 4 mg/kg in combination with methotrexate. These data demonstrated a statistically significant increase in the proportion of ACR20 responders in the tocilizumab 4 mg/kg treatment group compared with placebo, although the proportion of patients achieving this response was lower than that observed with the tocilizumab 8 mg/kg treatment group.

   Regarding safety, the 4 mg/kg dose of tocilizumab appeared to be associated with a lower incidence of serious infection than the 8 mg/kg dose when used in combination with a DMARD; no GI perforation events were reported in patients on 4 mg/kg. In the 24-week controlled period, 3 GI perforations occurred in patients on TCZ 8 mg/kg in compared to none on placebo or 4 mg/kg.

The Sponsor has proposed a dose regimen of 8 mg/kg every 4 weeks. If tocilizumab is approved, do you agree that this is the appropriate dose? Discuss whether there are patients at higher risk of adverse events for whom a lower dose should be recommended.

Most members agreed that the 4mg/kg dosing was effective and that dosing should start at 4mg/kg and increase to 8mg/kg if there is a clinical need.

Please see the transcript for detailed discussion.

3. In view of the data available for safety and efficacy, do you recommend approval of tocilizumab for the treatment of patients with moderately to severely active rheumatoid arthritis? (This is a voting question)

Vote : ***Yes=10*** ***No = 1*** ***Abstain = 0***

4. Depending on your response to Question 3, please address the following questions:

    a. For immunosuppressive products approved for RA, the FDA generally expects Sponsors to conduct postmarketing studies to assess safety of long-term treatment by continuing long-term treatment studies out to 5 years and to assess the effect of the product on responses to therapeutic vaccination. If you recommend approval, are there additional postmarketing studies the Sponsor should conduct to further assess the safety of the product?

The committee recommended having a large enough study to detect an increased risk of CVD and demyelination.

    b. If you recommend against approval, what additional data are needed to gain approval?

One member noted that more long term data was needed regarding infection, cardiovascular risks and liver enzyme abnormalities.

Please see the transcript for detailed discussion

The meeting adjourned at approximately 2:25 p.m.